NDA
21-506

DOCKET NO: 271988US0 SD

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IN RE PATENT OF	:
HIDENORI OHKI ET AL	: GROUP ART UNIT: 1654
SERIAL NO: 09/248,267	: EXAMINER: DAVENPORT, A. M.
FILED: FEBRUARY 11, 1999	: PATENT NO. 6,265,536
FOR: CYCLIC HEXAPEPTIDES HAVING ANTIBIOTIC ACTIVITY	: ISSUED: JULY 24, 2001

BEST AVAILABLE COPY

APPLICATION FOR EXTENSION OF PATENT TERM UNDER

35 U.S.C. § 156 AND 37 C.F.R. §§ 1.710, 1.720, 1.730, 1.740, 1.741, 1.750, 1.775 AND 1.785 (b)

MAIL STOP: PATENT TERM EXTENSION

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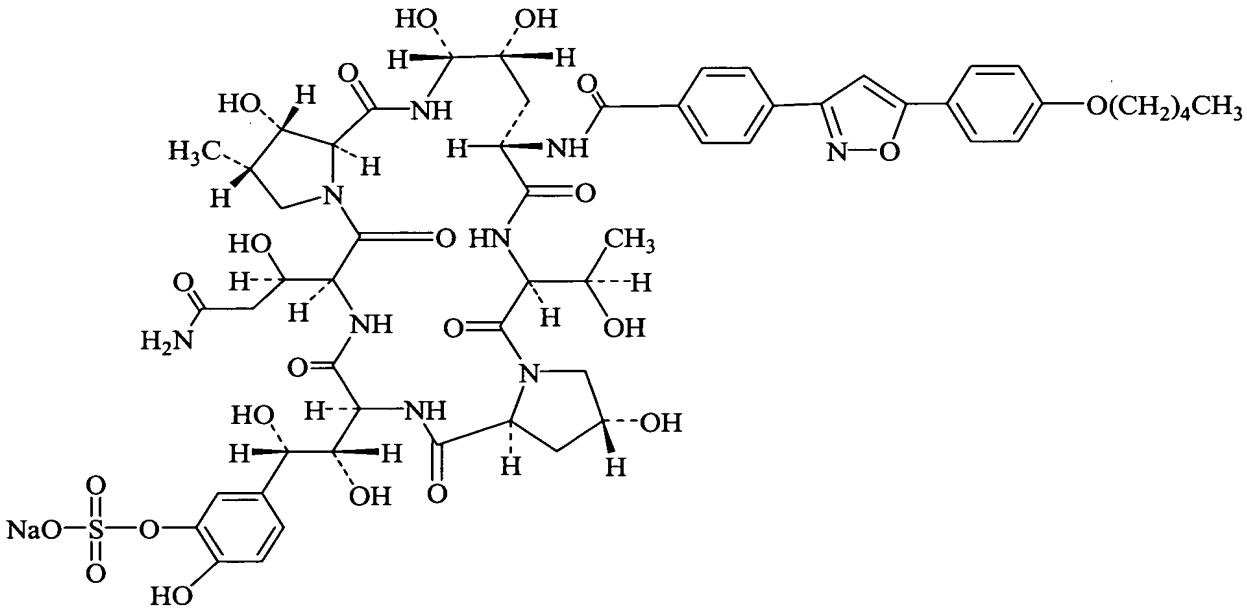
SIR:

This is an application for extension of patent term under 35 U.S.C. § 156 and 37 C.F.R. §§ 1.710, 1.720, 1.730, 1.740, 1.741, 1.750, 1.775 and 1.785 (b) for U.S. Patent No. 6,265,536 ("the '536 patent"), based on NDA 21-506.

Three additional copies of this application are being submitted herewith (37 C.F.R. § 1.740(b)).

I. Complete Identification of the Product (37 C.F.R. § 1.740(a)(1)).

The approved product is Mycamine, which is the registered name for injectable doses of lyophilized micafungin sodium. Each injectable dose contains 50 mg of the active ingredient: micafungin sodium. The chemical name for micafungin sodium is sodium 5-[(1S,2S)-2-[(3S,6S,9S,11R,15S,18S,20R,21R,24S,25S,26S)-3-[(R)-2-carbamoyl-1-hydroxyethyl]-11,20,21,25-tetrahydroxy-15-[(R)-1-hydroxyethyl]-26-methyl-2,5,8,14,17,23-hexaoxo-18-[4-[5-(4-pentyloxyphenyl)isoxazol-3-yl]benzoylamino]-1,4,7,13,16,22-hexaazatricyclo[22.3.0.$0^{9,13}$]heptacos-6-yl]-1,2-dihydroxyethyl]-2-hydroxyphenyl sulfate. The CAS Number is 179165-70-9. The molecular weight is 1292.27. The molecular formula is $C_{56}H_{70}N_9NaO_{23}S$, and it has the following structure:



Each dose of Mycamine contains 50 mg of micafungin sodium, 200 mg lactose, with citric acid and/or sodium hydroxide (used for pH adjustment).

II. Complete Identification of the Federal Statute Under which Regulatory Review Occurred (37 C.F.R. § 1.740(a)(2)).

Regulatory permission to sell Mycamine was granted under 21 U.S.C. § 355 (section 505 of the Federal Food, Drug, and Cosmetic Act).

III. Identification of the Date on which the Product Received Approval (37 C.F.R. § 1.740(a)(3)).

Regulatory approval for Mycamine, based on NDA 21-754, was approved on March 16, 2005, and a copy of the approval letter is attached hereto as Exhibit A.

IV. Identification of Each Active Ingredient and Statement that Each Active Ingredient has not been Previously Approved (37 C.F.R. § 1.740(a)(4)).

The sole active ingredient in the approved product is micafungin sodium. Micafungin sodium has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

V. Statement that Application is being Submitted within the Sixty Day Period (37 C.F.R. § 1.740(a)(5)).

This application is being submitted within the sixty day period specified by 35 U.S.C. § 156(1) and 37 C.F.R. § 1.720(f).

VI. Complete Identification of the Patent (37 C.F.R. § 1.740(a)(6)).

The patent for which extension of patent term is sought is U.S. Patent No. 6,265,536 ("the '536 patent"), which names Hidenori Ohki, Masaki Tomishima, Akira Yamada, and Hisashi Takasugi as inventors, and which issued on July 24, 2001, from U.S. Patent Application Serial No. 09/248,267, and is currently set to expire on September 29, 2015.

VII. A Copy of the Patent for which Extension of Term is being Sought (37 C.F.R. § 1.740(a)(7)).

A copy of the '536 patent is attached hereto as Exhibit B.

VIII. Copies of any Disclaimers, Certificates of Correction, Receipt of Maintenance Fee Payments, or Reexamination Certificates Issued in the Patent (37 C.F.R. § 1.740(a)(8)).

Applicants state on the record that no disclaimers have been filed in the '536 patent and that no certificates of correction or reexamination certificates have been issued in the '536 patent.

A copy of the receipt of maintenance fee payment for the first maintenance fee in the '536 patent is attached hereto as Exhibit C.

IX. Statement that the Patent Claims the Approved Product (37 C.F.R. § 1.740(a)(9)).

The approved product, Mycamine, injectable micafungin sodium, is claimed in the '536 patent.

The following chart sets forth the relationship between the claims of the '536 patent and the approved product.

Claim of the '536 Patent

1. A polypeptide compound of the following general formula (SEQ ID NO:1):

[structure of formula (I) omitted]

wherein R^1 is lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least ore oxygen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have one or more suitable substituent(s);

lower alkanoyl substituted with saturated 3 to 8 membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

ar(lower)alkenoyl substituted with aryl which may have one or more suitable substituent(s);

naphthyl(lower)alkenoyl which may have one or more higher alkoxy;

lower alkynoyl which may have one or more suitable substituent(s);

(C_2 –C_6)alkanoyl substituted with naphthyl having higher alkoxy;

ar(C_2-C_6)alkanoyl substituted with aryl having one or more suitable substituent(s), in which, ar(C2-C6)alkanoyl may have one or more suitable substituent(s);

aroyl substituted with heterocyclic group which may have one or more suitable

Mycamine

Mycamine contains micafungin sodium, which is the sodium salt of the compound of claim 1, when R^1 is "aroyl substituted with heterocyclic group which may have one or more suitable substituent(s), in which aroyl may have one or more suitable substituent(s)."

substituent(s), in which aroyl may have one or more suitable substituent(s);

aroyl substituted with aryl having lower alkoxy(higher)alkoxyl;

aroyl substituted with aryl having lower alkyl;

aroyl substituted with aryl having higher alkyl;

ar(lower)alkoxy(lower)alkanoyl which may have one or more suitable substituent(s);

arylamino(lower)alkanoyl which may have one or more suitable substituent(s);

lower alkanoyl substituted with pyrazolyl which has lower alkyl and aryl having higher alkoxy;

lower alkoxy(higher)alkanoyl, in which higher alkanoyl may have one or more suitable substituent(s);

aroyl substituted with cyclo(lower)alkyl having lower alkyl; indolylcarbonyl having higher alkyl;

naphthoyl having lower alkyl;

naphthoyl having higher alkyl;

naphthoyl having lower alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkoxy(lower)alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkoxy(lower)alkoxy;

aroyl substituted with aryl which has aryl having lower alkoxy(lower)alkoxy;

aroyl substituted with aryl having heterocyclicoxy(higher)alkoxy;

aroyl substituted with aryl having aryloxy(lower)alkoxy;

lower alkanoyl substituted with oxazolyl which has aryl having higher alkoxy;

higher alkanoyl having hydroxy;

higher alkanoyl having ar(lower)alkyl and hydroxy; or 3-methyl-tridecenoyl; and a pharmaceutically acceptable salt thereof.

4. A compound of claim 1, wherein

R^1 is aroyl substituted with heterocyclic group which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, phenyl having lower alkoxy(higher)alkoxy, phenyl having higher alkenyloxy, heterocyclic group substituted with phenyl having lower alkoxy, heterocyclic group, cyclo(lower)alkyl having phenyl, phenyl having cyclo(lower)alkyl, phenyl substituted with heterocyclic group having lower alkyl and oxo, cyclo(lower)alkyl having lower alkyl, phenyl substituted with phenyl having lower alkoxy, phenyl having heterocyclic group and oxo, in which aroyl may have halogen;

aroyl substituted with aryl having lower alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkyl; or aroyl substituted with aryl having higher alkyl.

Mycamine contains micafungin sodium, which is the sodium salt of the compound of claim 4, when R^1 is "aroyl substituted with heterocyclic group which may have 1 to 3 substituent(s) selected from the group consisting of . . . phenyl having lower alkoxy."

9. A compound claim 4, wherein

R^1 is benzoyl substituted with saturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkyl, phenyl having lower alkoxy(higher)alkoxy, phenyl having higher alkenyloxy, piperidyl substituted with phenyl having lower alkoxy, piperidyl, cyclo(lower)alkyl having phenyl, phenyl having cyclo(lower)alkyl, and phenyl substituted with triazolyl having oxo and lower alkyl,

in which benzoyl may have halogen;

benzoyl substituted with unsaturated 5-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkoxy(higher)alkoxy, and phenyl substituted with phenyl having lower alkoxy;

benzoyl substituted with 5 or 6-membered heteromonoccyclic group containing 1 or 2 nitrogen atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl and phenol having lower alkoxy;

benzoyl substituted with 5-membered heteromonocyclic group containing 1 to 2 nitrogen atom(s) and 1 to 2 sulfur atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, cyclo(lower)alkyl having lower alkyl, phenyl substituted with phenyl having lower alkoxy, phenyl having cyclo(lower)alkyl, phenyl having piperidine, and phenyl having lower alkoxy(higher)alkoxy;

Mycamine contains micafungin sodium, which is the sodium salt of the compound of claim 9, when R^1 is "benzoyl substituted with unsaturated 5-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of . . . phenyl having lower alkoxy."

benzoyl substituted with phenyl having lower alkoxy(higher)alkoxy;

benzoyl substituted with phenol having lower alkyl; or

benzoyl substituted with phenyl having higher alkyl.

16. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers or excipients.	Mycamine contains micafungin sodium, which is the sodium salt of the compound of claim 1, when R^1 is "aroyl substituted with heterocyclic group which may have one or more suitable substituent(s), in which aroyl may have one or more suitable substituent(s)."
17. A method for the prophylactic and/or the therapeutic treatment of infectious diseases caused by pathogenic microorganisms which may comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.	Mycamine contains micafungin sodium, which is the sodium salt of the compound of claim 1, when R^1 is "aroyl substituted with heterocyclic group which may have one or more suitable substituent(s), in which aroyl may have one or more suitable substituent(s)."

X. Statement of Relevant Dates and Information Pursuant to 35 U.S.C. § 156(g) for a human drug (37 C.F.R. § 1.740(a)(10)(i)).

(A) The Effective Date of the IND and the IND number (37 C.F.R. § 1.740(a)(10)(i)(A)).

The effective date for the IND for the approved product is February 26, 1998, and the IND number for the approved product is IND 55,322. However, the amended protocol, protocol 03-7-005, which is the basis for NDA 21-754, was not filed in IND 55,322 until June 30, 2003. Thus, for the purposes of this application, the regulatory review period did not begin until June 30, 2003.

(B) The Date on which the NDA was Initially Submitted and the NDA Number (37 C.F.R. § 1.740(a)(10)(B)).

The NDA for the approved product was initially submitted on April 23, 2004, and the NDA number for the approved product is 21-754.

(C) The Date on which the NDA was Approved (37 C.F.R. § 1.740(a)(10)(C)).

NDA 21-754 was approved on March 16, 2005.

XI. Brief Description of Significant Activity Undertaken by the Marketing Applicant During the Applicable Regulatory Review Period and the Significant Dates Applicable to Such Activities (37 C.F.R. § 1.740(11)).

A. The IND.

A list of significant activities undertaken by the marketing applicant during IND 55,322 and the significant dates applicable thereto is provided in Table 1 below.

The following abbreviations are used in Table 1:

ANR	Annual Report
BD	Briefing Document (white paper)
CLIN	Clinical Information Amendment
CMC	CMC Information Amendment
GC	General Correspondence (e.g. Cross Reference Letters, Briefing Documents)
PHAS4	Phase 4 Commitment Response
PRO	Protocol (e.g. draft, new, new and revised investigators, revised, amendment)
PT	Pharmacology and Toxicology Information Amendment
SAE	Safety Report (Initial and Follow-up)

Table 1.

DATE	TYPE	DESCRIPTION
3/28/05	GC	Transfer Letter
3/24/05	SAE	IND Safety Reports – Initial and Follow-up
3/15/05	SAE	IND Safety Report – Follow-up
3/2/05	SAE	IND Safety Report – Follow-up
3/1/05	PRO	Protocol Amendment: Revised Protocol 03-0-192 incorporating Amendment 4
2/17/05	SAE	IND Safety Reports – Initial and Follow-up
2/14/05	PRO	Protocol Amendment: New and Revised 1572s for Protocol 03-0-192
1/26/05	SAE	IND Safety Reports – Initial and Followup
1/12/05	PRO	Protocol Amendment: New and Revised 1572s for Protocol 03-0-192
12/22/04	SAE	IND Safety Report – Initial and Followup
12/7/04	PRO	Protocol Amendment: New and Revised 1572s for Protocol 03-0-192 and Revised Transfer of Obligations for -192
10/27/04	PRO	Protocol Amendment: New and Revised 1572s for Protocol 03-0-192 and FG-463-21-08
10/20/04	SAE	IND Safety Report - Followup
10/5/01	SAE	IND Safety Report - Initial
10/1/04	CMC	Info Amendment: CMC – notified FDA to cross reference NDA 21-506 and 21-754 for updated CMC information for FK463 drug product
9/30/04	PRO	Protocol Amendment: New and Revised 1572s for Protocol 03-0-192, Transfer of Obligations for -192
9/29/04	GC/PRO	Response to comments from FDA during 7/27/04 T-Con re: proposed closed testing procedure for study 03-0-192.
9/29/04	SAE	IND Safety Reports – F/U
9/17/04	SAE	IND Safety Report – Initial and F/U
9/9/04	SAE	IND Safety Report – Initial and F/U
9/1/04	PRO	Protocol Amendment: New Protocol 03-0-192, Amendments 1-3, Revised Protocol and Investigator Data (Sioson).
8/27/04	SAE	IND Safety Report – Initial

8/20/04	SAE	IND Safety Report – F/U
8/10/04	SAE	IND Safety Report – Initial and F/U
7/29/04	SAE	IND Safety Report – Initial
7/22/04	SAE	IND Safety Report – F/U
7/21/04	PRO	Protocol Amendment: Revised 1572s for Protocols 01-0-124 and FG-463-21-08
7/15/04	SAE	IND Safety Report – Initial and F/U
7/6/04	SAE	IND Safety Report – F/U
7/2/04	PRO	Response to FDA Response re: SPA for Protocol 03-0-192 (Amendment #2 and Revised Protocol)
6/23/04	SAE	IND Safety Report - Initial
6/10/04	ANR	Annual Report for reporting interval 11/27/02 – 11/26/03
6/3/04	SAE	IND Safety Report – F/U
5/28/04	PRO	Protocol Amendment: Revised 1572 for Protocol FG-463-21-08
5/26/04	SAE	IND Safety Report – Initial & F/U
5/24/04	PRO	Request for SPA – Clinical Protocol No. 04-0-199 (BAMSG #2-02) – included list of questions
5/11/04	SAE	IND Safety Report – Initial
4/29/04	SAE	IND Safety Report – Initial & F/U
4/28/04	PRO	Protocol Amendment: New Investigators for Protocol 03-7-005, Revised 1572s for Protocol FG-463-21-08 and 01-0-124
4/14/04	SAE	IND Safety Report – Initial & F/U
4/9/04	PRO	Special Protocol Assessment – Protocol 03-0-192 incorporating Amendment #1
4/8/04	SAE	IND Safety Report – Initial & F/U
4/7/04	SAE	IND Safety Report – F/U
4/7/04	PRO	Protocol Amendment: New Protocol 04-0-193, Admin Change #1, Transfer of Obligations, PI/CV for S. Reilley
3/30/04	SAE	IND Safety Report – Initial and F/U
3/18/04	SAE	IND Safety Report – Initial and F/U
3/16/04	PRO	Protocol Amendment: New Investigators for Protocol 03-7-005 and Revised 1572 for Protocol FG-463-21-08

3/10/04	SAE	IND Safety Report – Initial and F/U
2/19/04	SAE	IND Safety Report – F/U
2/5/04	PRO	Protocol Amendment: New Investigator for Protocol FG-463-21-08
1/30/04	SAE	IND Safety Report – F/U
1/20/04	SAE	IND Safety Report – F/U
1/9/04	PRO	Protocol Amendment: New Investigator for Protocol 98-0-047, Revised 1572s for FG-463-21-08, 01-0-124
1/8/04	SAE	IND Safety Report - Initial
12/23/03	SAE	IND Safety Report – Initial and Followup
12/10/03	SAE	Safety Report: Follow-up
12/5/03	PRO	Protocol Amendment: New Investigators for FG-463-21-08 and Revised Forms for same and 01-0-124
12/3/03	SAE	Safety Report: Initial
11/20/03	SAE	Safety Report: Follow-up
11/20/03	SAE	Safety Report: Initial
11/18/03	SAE	Safety Report: Follow-up
11/12/03	PRO	Submission of Micafungin Candidiasis Clinical Protocols (request of the FDA). 98-0-047, 03-7-005, FG-463-21-08, FG-463-21-09.
11/12/03	GC	Request for Pre-NDA Meeting
11/06/03	SAE	IND Safety Report: Initial
11/06/03	PRO	Protocol Amendment: New Investigators and Revised Forms 1572
11/04/03	SAE	IND Safety Report: Initial
10/30/03	SAE	IND Safety Report: Initial
10/28/03	SAE	IND Safety Report - Followup
10/24/03	BD	Briefing Document for New EC NDA (meeting to be held November 24, 2003)
10/23/03	SAE	IND Safety Report - Followup
10/22/03	CLIN	Addendum to Edition 4 of the IB
10/14/03	SAE	IND Safety Report - Initial

10/14/03	SAE	IND Safety Report - Followup
10/14/03	SAE	IND Safety Report - Initial
10/10/03	PRO	Protocol Amendment: Change in protocol 03-7-005 and draft IAP
9/30/03	SAE	IND Safety Report - Initial
9/29/03	PRO	Protocol Amendment: New Investigators and Revised 1572s
9/26/03	SAE	IND Safety Report - Followup
9/26/03	SAE	IND Safety Report - Followup
9/23/03	SAE	IND Safety Report - Initial
9/16/03	SAE	IND Safety Report - Followup
9/12/03	SAE	IND Safety Report - Followup
9/10/03	SAE	IND Safety Report - Initial
9/9/03	SAE	IND Safety Report - Followups
9/9/03	PRO	Protocol Amendment: New Protocols (03-0-175, 03-0-176, 03-0-177, 03-0-178), Admin Change 01 to all 4 protocols, Investigator Information.
9/5/03	SAE	IND Safety Report - Followup
9/3/03	SAE	IND Safety Report - Followup
08/29/03	PRO	Protocol Amendment: New Protocol (FG-463-21-08) and Investigator Information (McNeil)
08/28/03	SAE	IND Safety Report - Initial
08/27/03	SAE	IND Safety Report - Followup
08/21/03	SAE	IND Safety Report - Initial
08/20/03	SAE	IND Safety Report - Followup
08/14/03	SAE	IND Safety Report - Initial
08/12/03	SAE	IND Safety Report - Initial
08/08/03	SAE	IND Safety Report – Initial and Followup
08/07/03	SAE	IND Safety Report - Initial
08/01/03	SAE	IND Safety Report - Initial

07/30/03	SAE	IND Safety Report - Initial
07/24/03	SAE	IND Safety Report - Initial
07/18/03	SAE	IND Safety Report - Followup
07/09/03	SAE	IND Safety Reports: Initial and Followup.
07/03/03	GC	Proposal for New NDA Esophageal Candidiasis (Fujisawa's Proposal to Address Issues Raised in the Division's May 23, 2003 Letter concerning the Minimum 300 subjects receiving FK463 at a dose of 150 mg/day for 10 days).
06/30/03	PRO	Protocol Amendment: New Protocol 03-7-005
06/27/03	SAE	IND Safety Reports - Initial
06/25/03	PRO	Protocol Amendment: New Investigators for Protocol 01-0-124 and Revised Forms FDA 1572 for Protocols 98-0-046 and 01-0-124
6/17/03	SAE	IND Safety Reports - Initial
6/10/03	SAE	IND Safety Reports – Initial and Followup
6/3/03	SAE	IND Safety Reports - Followups
5/21/03	SAE	IND Safety Reports - Followups
5/16/03	PRO	Protocol Amendment: New Investigators and Revised Form FDA 1572 for 046, 124
5/6/03	SAE	IND Safety Reports – Initial
5/5/03	ANR	Annual Report 11/27/01-11/26/02
4/29/03	SAE	IND Safety Reports – Initial and Followup
4/18/03	SAE	IND Safety Reports – Initial and Followup
4/9/03	PRO	Protocol Amendment: New Investigators and Revised Form FDA 1572 for 046, 124, and 125
4/4/03	SAE	IND Safety Reports - Followup
3/26/03	PRO	Protocol Amendment: Amendment 02 to Protocol 01-0-124
3/21/03	SAE	IND Safety Report - Initial
3/14/03	SAE	IND Safety Reports -Followup
3/13/03	SAE	IND Safety Reports-Followup (FAX) Same as Serial 158 Hard-copy)
3/7/03	PRO	Protocol Amendment: New Investigators for 01-0-124

2/27/03	SAE	IND Safety Reports– Initial and Followup
2/18/03	SAE	IND Safety Reports- Initial
2/17/03	PRO	Protocol Amendment: New Investigators and Revised 1572 for 01-0-124
1/3/03	PRO	Protocol Amendment: New Investigator for 01-0-124 & revised 1572 for 98-0-047
12/13/02	PRO	Protocol Amendment: Revised Transfer of Obligations for -124 and -125
12/10/02	SAE	IND Safety Report - Followup
11/25/02	PRO	Protocol Amendment: Revised 1572s for 98-0-046 & 98-0-047
11/5/02	PRO	Protocol Amendment: New Protocol 01-0-125 & Investigator Information for N. Seibel
10/23/02	PRO	Protocol Amendment 1 to Protocol 01-0-124 and Investigator Information
10/3/02	PRO	Protocol Amendment: New Investigators for 98-0-046, 98-0-047 & 99-0-063; Revised 1572s for 98-0-046 & 98-0-047
9/27/02	ANR	Annual Report 11/27/00-11/26/01
9/26/02	SAE	IND Safety Report (15-day)
08/30/02	PRO	Protocol Amendment: Revised 1572s for 98-0-046 & 98-0-047
08/9/02	SAE	IND Safety Report (15-day)
07/31/02	PRO	Pre-emptive White Paper/Protocol 01-0-124 (received acknowledgement letter from FDA dated 10/8/02)
07/26/02	SAE	Follow-up IND Safety Report (15-day)
07/18/02	PRO	Protocol Amendment: Revised 1572s for 98-0-046, 98-0-047, and 99-0-063
06/14/02	SAE	Initial IND Safety Report (15 day)
5/10/02	PRO	Protocol Amendment – Revised 1572s for 98-0-046, 98-0-047, and 98-0-050
4/8/02	GEN	General Correspondence: Response to FDA's Fax dated 4/3/02 re: FHI's submission of proposed SAS datasets and data def files (Serial No. 132)
04/03/02	SAE	Follow-up IND Safety Report (15-day)
03/15/02	PRO	Protocol Amendment – New Investigator (Myint) for 98-0-046; Revised 1572s for 98-0-046, 98-0-047, and 99-0-063
03/13/02	SAE	Initial IND Safety Report (15-day)
03/08/02	GEN	Submission of Proposed Archival SAS datasets and data definition files (–050 Study) and proposed SAS datasets (SHAM) for Reviwer Aids
02/28/02	SAE	Follow-up IND Safety Report (15-day)

02/15/02	PRO	Protocol Amendment – New Investigators/CVs and Revised 1572s for 98-0-046, 98-0-047, 98-0-050. Revised 1572s for 01-0-110 and 01-0-111.
02/12/02	SAE	Initial IND Safety Report (15-day)
01/16/02	PRO	Protocol Amendment – New Investigators and Revised 1572s for 98-0-046, 98-0-047
11/09/01	PRO	Protocol Amendment – New Investigators for 98-0-046, 98-0-047, 01-0-110, 01-0-111
11/8/01	GC	Request for Meeting with Stat and Medical Reviewers to discuss proposed SAS datasets and proposed format of data definition files (submitted on CD-ROM)
10/26/01	GC	Summary of micafungin dosing
10/12/01	PRO	Protocol Amendment: New Investigators to 98-0-046 98-0-057, 98-0-050 , 99-0-063 and revised 1572s
9/20/01	PRO	Protocol Amendment: New Protocols (01-0-105, 110, 111) and 1572/CV Information for each protocol
8/29/01	PRO	Protocol Amendment: New Protocol (01-0-104) and 1572/CV for S. Austin
8/28/01	SAE	Follow-up IND Safety Report (15-day)
8/3/01	SAE	Initial IND Safety Report (15-day)
7/13/01	SAE	Initial IND Safety Report (15-day)
7/5/01	GEN	Submission of e-mail correspondence between R. Reed (FHI) and L. Chan (FDA). Communications dated 6/29/01 and 7/03/01
6/29/01	GEN	Submission of 4 Draft Protocol Synopses
6/14/01	PRO/IB	Submission of Revised IB and Amendment 2 to Protocol 99-0-063
6/13/01	SAE	IND F/U Safety Report
6/1/01	PRO	Protocol Amendment-New Investigators and Revised 1572s
5/29/01	SAE	IND Safety Alert Report
5/18/01	SAE	IND Safety Alert Report
4/19/01	BRFDOC	Submission of Pre-NDA Briefing Document
4/6/01	GC	Request for a teleconference
4/3/01	PRO	Protocol Amendment: New and revised 1572s
4/3/01	ANR	Annual Report
2/20/01	PRO	Protocol Amendment: New and revised 1572s
12/27/00	PRO	Protocol Amendment: New and revised 1572s

12/12/00	SAE	15-day Alert Report
11/16/00	PRO	New protocol (99-0-063) and investigator to it.
11/15/00	SAE	15-day Alert Report
11/6/00	PRO	Protocol Amendment: new and revised 1572s
10/27/00	SAE	15-day Alert Report
9/21/00	PRO	Protocol amendment: new and revised 1572s.
8/22/00	SAE	15-day Alert Report
8/4/00	SAE	15-day Alert Report
7/31/00	PRO	Protocol Amendment: New and revised 1572s.
7/7/00	PRO	Protocol Amendment: New Investigators
6/9/00	SAE	15-day Alert Report
6/6/00	AMEND	Information Amendment: Clinical pK study for 98-0-040
5/30/00	PRO	Protocol Amendment: New Investigators
5/9/00	SAE	15-day Alert Report
5/5/00	PRO	Protocol Amendment: New Investigators and revised information to 98-0-046, 98-0-047, and 98-0-050
5/3/00	PRO	Protocol Amendments: Change in protocol 98-0-046 and 98-0-047 (Amendments 4)
04/12/00	PRO	Protocol Amendment: New Investigators and revised 1572s to 98-0-050, 98-0-046 and 98-0-047
03/22/00	PRO	Protocol Amendment: New Investigators
03/07/00	AMEND	Amendment to Annual Report; submitted two stability reports RAR000097 and RAR000098
03/01/00	SAE	15-day Alert Report
03/01/00	ANR	Annual Report 11/27/98 to 11/26/99
02/28/00	PRO	Protocol Amendment: New Investigators to 98-0-050, 98-0-046 and 98-0-047
02/25/00	SAE	15-day Alert Report
02/15/00	PRO	Protocol Amendment: New Investigators to 98-0-050 and revised 1572s
02/11/00	SAE	15-day Alert Report
02/10/00	SAE	15 day alert report

02/02/00	SAE	Follow-up safety report
01/26/00	AMEND	Information Amendment: Clinical pK study L1999000044 for Protocol 97-0-041
01/20/00	SAE	Initial safety report
01/19/00	PRO	Protocol Amendment: New Investigators to 98-0-050
01/05/00	PAE	15-day Alert report
12/20/99	PRO	Protocol Amendment: New investigators to 98-0-050
12/15/99	AMEND	CMC Amendment to the drug product
12/9/99	SAE	IND Safety report submitted to FDA for one initial report
12/9/99	PRO	Protocol Amendment: New Investigators to 98-0-046, 98-0-047 and 98-0-050
12/8/99	AMEND	Information Amendment: Clinical. Final report for Protocol 97-0-041 entitled "A phase I/II study to determine the maximum tolerated dose and pharmacokinetics of FK463 in combination with fluconazole for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant."
12/3/99	SAE	15-day Follow-up Safety Report
11/30/99	LTR	General Correspondence : Request to FDA to review Drug Master File
11/10/99	PRO	Protocol Amendment: New investigators to 98-0-046 and 98-0-047
11/04/99	SAE	Two IND initial safety reports submitted to FDA
11/03/99	PRO	Protocol Amendment: Change in Protocol 98-0-043: to increase dose to be evaluated to include 3.0 and 4.0 mg/kg/day and administrative changes
10/28/99	PRO	Protocol Amendment: New Protocol (98-0-050), Amendment 01 and first investigator
10/26/99	LTR	Response to FDA EOP2 Meeting minutes from 9/10 meeting
10/22/99	SAE	1 initial report
10/19/99	PRO	Protocol Amendment: New Investigators to 97-0-047
10/05/99	SAE	IND Safety Report: 1 follow-up safety report submitted to FDA
09/14/99	PRO	Protocol Amendment: New Investigators to 98-0-043, 98-0-046 and 98-0-047
09/17/99	SAE	IND Safety Reports – 2 initial reports submitted to FDA
09/02/99	LTR	Additional Information for EOP2 Meeting: Revision to question #5

08/25/99	LTR	End of Phase 2 Meeting Agenda and List of Attendees for FHI
08/24/99	SAE	IND Safety Report – 1 follow up report
08/11/99	PRO	Protocol Amendment: New Investigators.
08/05/99	LTR	End of phase 2 Briefing Document
08/05/99	SAE	15 day /alert report
07/20/99	AMEND	Information Amendment: Pharm./Tox Report GLR980160
07/13/99	PRO	Protocol Amendment: New Investigators to: 98-0-046 and 98-0-47
07/01/99	PRO	Protocol Amendment: New Investigators New investigators to 98-0-046 and 98-0-047.
06/30/99	AMEND	Information Amendment: Pharm./Tox. Reports CRD980156, CRD980083, GLR980003, CRD980043 and GLR980004.
06/29/99	SAE	IND Safety Report – follow-up report submitted to FDA
06/23/99	SAE	IND Safety Reports – follow-up reports submitted to FDA
06/09/99	PRO	Protocol Amendment: Change in Protocol Change in protocol 98-0-042 (to increase dose to 2.0 mg/kg/day, the rationale for doing so and administrative changes.
06/09/99	PRO	Protocol Amendment: Change in Protocol Change in European protocols FG463-21-01 and FG463-21-02
06/09/99	PRO	Protocol Amendment: New Investigators New investigators added to Protocol 98-0-046 and 98-0-047
05/20/99	SAE	IND Safety Report
05/06/99	PRO	Protocol Amendment: New Investigators New investigators added to Protocol 98-0-046 and 98-0-047.
05/05/99	SAE	IND Safety Report – initial report submitted to FDA
04/30/99	PRO	Protocol Amendment: Change in Protocols Change in Protocol 98-0-046, increase initial dose to 75 mg/day, etc. To 98-0-047, dose adjustments to 150 mg/day, etc.
04/14/99	PRO	Protocol Amendment: New Investigators Protocol 98-0-046 and Protocol 98-0-047
04/02/99	PRO	Protocol Amendment: New Investigators

		New Investigators added to protocol 98-0-047
03/30/99	AMEND	Information Amendment: Pharmacology/ Toxicology: FK463 and an amendment to the final report, 4 week IV toxicity study of FR179463 in rats with recovery study (GLR970116); a copy of report GLR980020 re: Single dose IV toxicity study of photo-degradated FK463 product in rats.
03/26/99	LTR	Response to FDA fax dated 1/19/99 Response to the FDA fax of 1/1/9/99 re: 4 attachments, agency's comments and FHI responses, QC sample data for studies CLR980023 and CLR980025; report titled PK of FK463 in Phase I repeated dose study; survival data that support ED50 values in reports CRR980116 and CRR980117.
03/24/99	PRO	Protocol Amendment: Change in Protocol Letter sent to FDA on 3/24/99 re: Change in Protocols 98-0-046 and 98-0-047 for exclusion of de novo patients at Canadian sites.
03/23/99	PRO	Protocol Amendment: New Investigator 98-0-046 and 98-0-047 .
03/16/99	LTR	FHI Meeting Minutes Minutes of 2/5/99 teleconference with FDA
03/16/99	PRO	Protocol Amendment: New Investigator Protocol 98-0-046 and 98-0-047
03/15/99	ANR	Annual Report Reporting interval 03/26/98 to 11/26/98
03/11/99	PRO	Protocol Amendment: New Investigator Protocol 98-0-043
03/03/99	SAE	IND Safety Report One initial safety report submitted on 3/3/99
03/02/99	PRO	Protocol Amendment: New Investigators Protocols 98-0-046 and 98-0-047;
02/23/99	PRO	Protocol Amendment: New Protocols, Protocol Amendment and New Investigator Protocol 98-0-047 "An Open-Label, Non-comparative Study of FK463 in the Treatment of Candidemia or Invasive Candidiasis", Amendment 01 to adjust the initial dose, to update the reconstitution procedures and to include regulatory agencies in addition to FDA; Protocol FG463-21-02 (European of same name as 98-0-047); and new investigator
02/23/99	GC	Response to FDA Letter FHI response to 12/4/98 letter regarding Serial numbers 014 and 015
02/12/99	PRO	Protocol Amendment: Change in protocol Amendment #4 Increase dose to be evaluated to 200 mg (protocol 97-0-041)

02/03/99	PRO	Protocol Amendment: New Protocol, amendment and New Investigator: Protocols 98-0-046 (US) and FG463-21-01 (European) "An Open-Label Non-Comparative Study of FK463 for the Treatment of Invasive Aspergillosis:, Amendment 01 to 98-0-046 and New Investigator.
01/20/99	GC	General Correspondence End-of-Phase 2 Meeting Request for mid-April
01/07/99	PRO	Protocol Amendment: New Investigator Protocol 97-0-041, Dr. Pranatharthi Chandrasekar
12/28/98	PRO	Protocol Amendment: New DRAFT Protocol Protocol 98-0-050 "A Phase III Randomized Double Blind Comparative Trial of FK463 versus Fluconazole for Prophylaxis of Fungal Infections in Patients Undergoing Bone Marrow or Peripheral Stem Cell Transplantation
12/07/98	PRO	Protocol Amendment: New Investigator N. Chao to 97-0-041
11/20/98	PRO	Protocol Amendment: New Investigator P. Flynn to 98-0-043
11/19/98	AMEND	Information Amendment: CMC Labeling change to clinical trial labels
11/13/98	PRO	Protocol Amendment: New Investigator T. Walsh to Protocol 98-0-043
11/4/98	PRO	Protocol Amendment: Change in protocol Change to 97-0-041; Amendment 03 increase dose from 100 mg/day to 150 mg/day
10/28/98	PRO	Protocol Amendment: New Protocol 98-0-043, Amendment 01 to this protocol and new investigator (Nita Seibel).
10/26/98	SAE	IND Safety Report
10/8/98	PRO	Protocol Amendment: New Investigators S. Devine and D. Simpson to 97-0-041
10/6/98	AMEND	Information Amendment: Clinical 2 non-IND clinical trial reports CLR980023 (R98-0224-463-C1-E) Phase 1 Single-Dose Intravenous Administration Study of FK463; CLR980025 (R98-0223-463-C1-E) Phase 1 Repeated Dose Intravenous Administration Study of FK463.
10/6/98	AMEND	Information Amendment - Pharm/Tox Three Non-clinical Reports: CRR980115 (R98-0200-463-P1-E) Prophylactic effect of FK463 against Pneumocystis carinii infection in mice. CRR980116 (R98-0201-463-P1-E) Efficacy of intravenous injection of FK463 in mouse models of pulmonary candidiasis and aspergillosis. CRR980117 (R98-0202-463-P1-E) Efficacy of intravenous injection of FK463 in mouse models of disseminated candidiasis and aspergillosis
8/4/98	PRO	Protocol Amendment: Change in Protocol 97-0-041 Amendment 2:

		Enrollment of allogeneic bone marrow or peripheral stem cell transplant patients.
7/6/98	AMEND	Information Amendment Response to May 1 letter of request and recommendations
6/15/98	PRO	Protocol Amendment – New Investigator New 1572s to 97-0-041 P. Cagnoni and J. Hiemenz
6/8/98	PRO	Protocol Amendment Change in Protocol 97-0-040 and an addendum to the Informed Consent Form.
6/3/98	LTR	Change in Corporate Name to FHI
5/14/98	PRO	Protocol Amendment – New Investigator To protocol 97-0-040 J. Kisicki
5/15/98	AMEND	Information Amendment - Pharm./Tox. 6 reports for as pharmacological and metabolic support: CRD980078, CRD980079, CRD980084, GLR980047, GLR980049 and GLR980048
4/13/98	PRO	Protocol Amendment Submission of requested information - 14-C Study, Informed Consent and amount of radiation per patient. (4/21/98 - This was returned by FDA as it was sent to the Fishers Lane address via Fed. Ex. By direction of A. Chun. Fishers Lane does not accept Fed. Ex. Packages. Was resubmitted to the Division via Fed. Ex
4/1/98	PRO	Protocol Amendment Revised protocol 97-0-041 to clarify the collection and processing of blood samples for pharmacokinetics analysis
02/26/98	IND	Original IND

B. The NDA.

A list of significant activities undertaken by the marketing applicant during the review of NDA 21-754 and the significant dates applicable thereto is provided in Table 2 below.

The following abbreviations are used in Table 2:

AMEND	Amendment to NDA or sNDA
ANR	Annual Report
FIELD	District Office Copy of CMC Supplement
GC	General Correspondence (e.g. Cross Reference Letters, Briefing Documents)
PHAS4	Phase 4 Commitments
PSUR	Periodic Safety Update Report
SUPL	Supplement

Table 2.

DATE	TYPE	DESCRIPTION
4/15/05A	GC	Forms FDA 3542 – Patent Information for Mycamine desk copies sent to Christina Chi (faxed to division on 4/15/2005)
4/15/05	SUPL	Changes Being Effected – Supplement (CBE-30 Alternative-Closure Configuration)
4/4/05	GC	Acceptance Letter
3/31/05	GC/LABEL	Submission of FPL (FHI) as required in approval letter (submitted electronically to both NDA 21-506 and 21-754). This represents the last submission to NDA 21-754 – all future submissions will be submitted to NDA 21-506 only
	GC	Transfer Letter

DATE	TYPE	DESCRIPTION
3/10/05A	GC	Submission of proposed press release for review and comment (including current draft PI dated 3/7/05). Note document was also submitted to DDMAC for their review and comment as well.
3/10/05	AMEND	Submitted latest versions of draft labeling - PI dated 3/7/05 and Vial/Carton dated 3/10/05 as submitted via e-mail (Submitted electronically to both NDA 21-754 and 21-506)
3/9/05	AMEND	Submitted latest versions of draft labeling - PI dated 3/7/05 and Vial/Carton dated 2/24/05 as submitted via e-mail (Submitted electronically to both NDA 21-754 and 21-506)
3/8/05	AMEND	Response to 3/4/05 e-mail request – Prophylaxis Efficacy Results (Submitted electronically to both NDA 21-754 and 21-506)
2/22/05	AMEND	Response to FDA Request for Information dated 2/21/05 (item-by-item response to comments raised by Microbiologist in a 3/23/03 e-mail). Also included in submission were the draft carton and container labeling for Mycamine (50 mg strength), which incorporated comments from the Division during 2/18/05 discussion.
2/18/05	AMEND	Response to FDA Request for Information dated 2/17/05 regarding reevaluation of Serious Hepatic Adverse Events and Hepatic Laboratory Changes.
2/11/05	AMEND	Response to Info Request Dated 2/4/05 (Division re-defined request on 2/10) and Response to Item 2 in 2/7/05 e-mail request. Submitted electronically to both NDA 21-754 and 21-506.

DATE	TYPE	DESCRIPTION
2/4/05A	AMEND	Response to FDA E-Mail request dated 2/3/05 (info re: Study -050). Complete response with exception requested SAS dataset
2/4/05	AMEND	Response to FDA E-Mail request dated 2/2/05 (clinical). Also included patient narratives requested in 2/1/05 request. Submitted electronically to both NDA 21-754 and 21-506
2/3/05	AMEND	Submission of FDA Form 3542a (Patent Certification) for new patent for Mycamine and statement to FDA that Fujisawa does NOT wish to pursue commercialization of the 25 mg product formulation at this time. Submitted electronically to both NDA 21-754 and 21-506
2/2/05	AMEND	Response to FDA E-mail request dated 2/1/05 – Response submitted electronically to both NDA 21-754 and 21-506
1/27/05	AMEND	Response to FDA Request for Information Dated 1/26/05 (E-mail from Dr. Singer). Also included was final compatibility report requested on 1/14/05, official submission of Medwatch forms requested 1/24/05 and proposed vial/carton labeling requested 1/25/05
1/26/05	AMEND	Final Response to FDA Info Request Dated 12/14/04 (Clinical) – completes the response to this request (submitted to both NDA 21-754 and 21-506)
1/10/05B	AMEND	Response to FDA Request for Information Dated 1/6/05 from Biostats Reviewer – Datasets submitted in SAS format (as requested) to NDA 21-754
1/10/05A	AMEND	Response to FDA Request for Information Dated 1/5/05 from Clinical Reviewer – Response submitted in full (electronically) to both NDA 21-754 and 21-506
1/10/05	AMEND	Response to FDA Request for Information Dated 1/3/05 from Clinical Reviewer – Response submitted in full (electronically) to both NDA 21-754 and 21-506
1/6/05	AMEND	Response to FDA Request for Information dated 12/22/05 from Clinical Reviewer (additional safety information and datasets for patients across several studies). Sent to both NDA 21-506 and 21-754
12/23/04	AMEND	Partial response to FDA Request for Information Dated 12/21/04 (Fax from Clinical Reviewer) – response submitted in full (electronically) to both NDA 21-506 and 21-754 (submission of requested datasets were NOT included)
12/22/04	AMEND	Response to FDA Request for Information Dated 12/14/04 (Fax from Clinical Reviewer) – response submitted in full (electronically) to both NDA 21-506 and 21-754. It was noted that several items would be submitted under separate cover when available.
12/1/04	AMEND	Response to FDA Request for Information Dated 10/27/04 from Clinical Reviewer (Item #2 – Expert Hematologist

DATE	TYPE	DESCRIPTION
		Panel Review)
11/18/04	AMEND	Response to FDA Request for Information Dated 11/15/04 from Clinical Reviewer
11/12/04	AMEND	Response to FDA Request for Information Dated 10/27/04 from Clinical Reviewer (except for Item #2)
10/20/04	AMEND	Response to FDA Request for Information Dated 10/19/04 from Chemistry & Microbiology Reviewers
10/1/04	GC	Submitted copy of IND Serial submission (Serial No. 262) submitted to provide for cross reference information to NDAs 21-506 and 21-754 for drug product
9/22/04	AMEND	Response to FDA's September 10, 2004 Request for Additional Clinical Information (full response).
8/24/04	AMEND	Submission of Section 9: 120-day Safety Update and Updated Labeling (package insert) – FSR for 03-7-005 and FG14 were also included
5/11/04	AMEND	Updated Patent Certification/Information on Forms 3542a (3 patents were submitted) submitted to NDA
4/23/04	ORIGINAL	Submission of Original NDA (electronic DLT Tape submitted to FDA) – no hard copies provided

XII. Statement that in the Opinion of the Applicant the Patent is Eligible for Extension of Patent Term and Statement as to the Length of extension and how the Length was Determined (37 C.F.R. § 1.740(a)(12)).

In the opinion of the applicant, the '536 patent is eligible for extension. In the opinion of the applicant, the '536 patent is entitled to an extension of 476 days, *i.e.*, the '536 patent is entitled to an extended expiration date of January 17, 2017. The extension of 476 days was calculated by the method described in 37 C.F.R. § 1.775.

The number of days by which the '536 patent should be extended was calculated as follows:

A. The minimum number of days in the regulatory review period was calculated according to 37 C.F.R. § 1.775(c) and reduced as appropriate pursuant to 37 C.F.R. §§ 1.775(d)(1)-(6).

B. The minimum number of days in the regulatory review was calculated by adding the number of days pursuant to (37 C.F.R. § 1.775(c)(1)) and the minimum number of days pursuant to (37 C.F.R. § 1.775(c)(2)).

C. The number of days pursuant to (37 C.F.R. § 1.775(c)(1)) was calculated as the number of days in the period starting from the date on which IND 55,322 was amended to include the protocol on which NDA 21-754 was based, June 30, 2003, and ending on the date NDA 21-754 was submitted, April 23, 2004, and determined to be 298 days.

D. The minimum number of days pursuant to (37 C.F.R. § 1.775(c)(2)) was calculated as the number of days in the period starting from the date NDA 21-754 was submitted, April 23, 2004, and ending on the date of approval of NDA 21-754, March 16, 2005, and determined to be at least 327 days.

E. Thus, the minimum number of days in the regulatory review was calculated by adding 298 days to 327 days and determined to be 625 days

F. The number of days to be subtracted from the regulatory review period under 37 C.F.R. § 1.775(d)(1) was calculated by determining the number of days pursuant to each of C.F.R. §§ 1.775(d)(1)(i)-(iii).

G. Since the regulatory review period began on June 30, 2003, and since the '536 patent issued on July 24, 2001, 0 days in the regulatory review period were on or before the date on which the '536 patent issued. Thus, the number of days pursuant to C.F.R. § 1.775(d)(1)(i) was determined to be 0.

H. As set forth above, applicants have acted with due diligence during the entire regulatory review period. Thus, the number of days pursuant to C.F.R. § 1.775(d)(1)(ii) was determined to be 0.

A. The number of days pursuant to C.F.R. § 1.775(d)(1)(iii) was calculated by dividing the number of days pursuant to 37 C.F.R. § 1.775(c)(1), 298 days, in half and determined to be 149 days.

I. The number of days pursuant to C.F.R. § 1.775(d)(1) was calculated by subtracting the number of days calculated pursuant to C.F.R. § 1.775(d)(1)(iii), 149 days, from the number of days calculated pursuant to C.F.R. § 1.775(c), 625 days, and determined to be 476 days.

J. The term of the '536 patent as extended as determined by C.F.R. § 1.775(d)(2) was calculated by adding the number of days calculated pursuant to C.F.R. § 1.775(d)(1), 476 days, to the original term of the '536 patent (current expiration date September 29, 2015) and determined to be January 17, 2017.

K. The term of the '536 patent as extended as determined by C.F.R. § 1.775(d)(3) was calculated by adding 14 years to the date of approval, March 16, 2005, and determined to be March 16, 2019.

L. The term of the '536 patent as extended as determined by C.F.R. § 1.775(d)(4) was calculated by comparing the dates calculated pursuant to C.F.R. § 1.775(d)(3) and C.F.R. § 1.775(d)(4) and selecting the earlier date and determined to be January 17, 2017.

M. The term of the '536 patent as extended as determined by C.F.R. § 1.775(d)(5)(i) was calculated by adding five years to the original expiration date of the '536 patent (September 29, 2015) and determined to be September 29, 2020.

N. The term of the '536 patent as extended as determined by C.F.R. § 1.775(d)(5)(ii) was calculated by selecting the earlier date pursuant to C.F.R. § 1.775(d)(4) and C.F.R. § 1.775(d)(5)(i) and determined to be January 17, 2017.

O. Since the '536 patent issued after September 24, 1984, no adjustment was made under C.F.R. § 1.775(d)(6).

XIII. Statement that Applicant Acknowledges a Duty to Disclose any Information which is Material to the Determination of the Entitlement to the Extension Sought (37 C.F.R. §§ 1.740(a)(13) and 1.765).

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

It is understood that the duty of candor and good faith toward the Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture rests on the patent owner or its agent, on each attorney or agent who represents the patent owner and on every other individual who is substantively involved on behalf of the patent owner in a patent term extension proceeding. All such individuals who are aware, or become aware, of material information adverse to a determination of entitlement to the extension sought, which has not been previously made of record in the patent term extension proceeding must bring such information to the attention of the Office or the Secretary, as appropriate, as soon as it is practical to do so after the individual becomes aware of the information. Information is material where there is a substantial likelihood that the Office or the Secretary would consider it important in determinations to be made in the patent term extension proceeding. 37 C.F.R. § 1.765(a).

It is also understood that disclosures pursuant to this section must be accompanied by a copy of each written document which is being disclosed. The disclosure must be made to the Office or the Secretary, as appropriate, unless the disclosure is material to determinations to be made by both the Office and the Secretary, in which case duplicate copies, certified as such, must be filed in the Office and with the Secretary. Disclosures pursuant to this section may be made to the Office or the Secretary, as appropriate, through an attorney or agent having responsibility on behalf of the patent owner or its agent for the patent term extension

proceeding or through a patent owner acting on his or her own behalf. Disclosure to such an attorney, agent or patent owner shall satisfy the duty of any other individual. Such an attorney, agent or patent owner has no duty to transmit information which is not material to the determination of entitlement to the extension sought. 37 C.F.R. § 1.765(b).

It is further understood that no patent will be determined eligible for extension and no extension will be issued if it is determined that fraud on the Office or the Secretary was practiced or attempted or the duty of disclosure was violated through bad faith or gross negligence in connection with the patent term extension proceeding. If it is established by clear and convincing evidence that any fraud was practiced or attempted on the Office or the Secretary in connection with the patent term extension proceeding or that there was any violation of the duty of disclosure through bad faith or gross negligence in connection with the patent term extension proceeding, a final determination will be made that the patent is not eligible for extension. 37 C.F.R. § 1.765(c).

In compliance of the duty of disclosure, it is acknowledged that additional applications for term extension for two additional patents based on the same regulatory review are also being filed. Specifically:

1. An application for term extension based on the regulatory review of Mycamine under NDA 21-506 was filed for U.S. Patent No. 6,107,458 (attorney docket no. 271987US0SD) on May 12, 2005;

2. An application for term extension based on the regulatory review of Mycamine under NDA 21-506 is also being filed for U.S. Patent No. 5,376,634 (attorney docket no. 270677US0SD);

3. An application for term extension based on the regulatory review of Mycamine under NDA 21-506 is also being filed for U.S. Patent No. 6,265,536 (attorney docket no. 271988US0SD);

4. An application for term extension based on the regulatory review of Mycamine under NDA 21-754 is also being filed for U.S. Patent No. 5,376,634 (attorney docket no. 272498US0SD); and

5. An application for term extension based on the regulatory review of Mycamine under NDA 21-506 is also being filed for U.S. Patent No. 6,107,634 (attorney docket no. 272499US0SD).

XIV. Prescribed Fee (37 C.F.R. § 1.740(a)(14)).

The fee as prescribed in 37 C.F.R. § 1.20(j)(2) is attached hereto in the from of a credit card form for the amount of $1120.00.

XV. Correspondence Information (37 C.F.R. § 1.740(a)(15)).

All inquiries and correspondence should be sent to:

Customer Number: 22850

Which corresponds to:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
1940 Duke Street
Alexandria, VA 22314

Telephone: 703-413-3000
Facsimile: 703-413-2220

XVI. Power of Attorney (37 C.F.R. §§ 1.730(a)(2) and (d)).

A copy of the original Power of Attorney is being submitted herewith as Exhibit D.

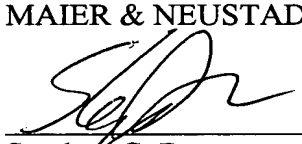
As can be seen from the face of the '536 patent itself, the '536 patent was originally assigned to Fujisawa Pharmaceutical Co., Ltd., of Osaka, Japan ("Fujisawa"). Effective April

1, 2005, Fujiswa became part of Astellas Pharma Inc., of Tokyo, Japan. A formal notice of the change of name has already been filed in the USPTO, and copies if the papers filed are attached hereto as Exhibit E. Oblon, Spivak, McClelland, Maier & Neustadt, P.C., remains the attorney of record for the '536 patent.

In view of the foregoing, Applicants submit that the present patent is entitled to the requested extension of patent term, and early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Stephen G. Baxter
Attorney of Record
Registration No. 32,884

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413-2220
(OSMMN 08/03)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-506
NDA 21-754

Fujisawa Healthcare, Inc.
Attention: Mr. Robert M. Reed
Associate Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015-2548

Dear Mr. Reed:

Please refer to your new drug application (NDA) dated April 29, 2002, received April 29, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mycamine™ (micafungin sodium) for Injection, 50 mg, NDA 21-506. The August 24, 2004 submission, received August 25, 2004, constituted a complete response to our January 29, 2003 approvable letter.

We acknowledge receipt of your submissions to NDA 21-506 dated:

October 1, 2004	December 23, 2004	February 9, 2005
October 15, 2004	January 6, 2005	February 11, 2005
October 20, 2004	January 10, 2005 (2)	February 15, 2005
October 25, 2004	January 26, 2005	February 28, 2005
October 29, 2004	January 27, 2005	March 8, 2005
November 12, 2004	February 2, 2005	March 9, 2005
December 1, 2004	February 3, 2005	March 10, 2005 (2)
December 22, 2004	February 4, 2005 (2)	

We also refer to your new drug application dated April 23, 2004, received April 26, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mycamine™ (micafungin sodium) for Injection, 50 mg, NDA 21-754.

We acknowledge receipt of your submissions to NDA 21-754 dated:

May 11, 2004	December 22, 2004	February 4, 2005 (2)
August 24, 2004	December 23, 2004	February 11, 2005
September 22, 2004	January 6, 2005	February 18, 2005
October 1, 2004	January 10, 2005 (3)	February 22, 2005
October 20, 2004	January 26, 2005	February 28, 2005
November 12, 2004	January 27, 2005	March 8, 2005
November 18, 2004	February 2, 2005	March 9, 2005
December 1, 2004	February 3, 2005	March 10, 2005 (2)

These new drug applications provide for the use of Mycamine™ (micafungin sodium) for Injection, for prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation (NDA 21-506) and for the treatment of esophageal candidiasis (NDA 21-754).

We completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved NDAs 21-506 and 21-754.**" Approval of these submissions by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring the pediatric study requirement for ages 0 to 16 years for prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation and for the treatment of esophageal candidiasis.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

1. Deferred pediatric study under PREA for the prophylaxis of *Candida* infections in patients ages 0 to 16 years old undergoing hematopoietic stem cell transplantation,

2. Deferred pediatric study under PREA for the treatment of esophageal candidiasis in patients ages 0 to 16 years old.

Final Report Submissions: March 30, 2010

Submit final study reports to NDA 21-506 only. For administrative purposes, all submissions related to these pediatric postmarketing study commitments must be clearly designated "**Required Pediatric Study Commitments.**"

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Special Pathogen and Immunologic Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 21-506 for this drug product, not to NDA 21-754. In the future, do not make submissions to NDA 21-754 except for the final printed labeling requested above.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, please call Christina H. Chi, Ph.D., Regulatory Health Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, M.D., M.P.H.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:

1. text for the package insert,
2. immediate container
3. carton labels

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Edward Cox
3/16/05 12:54:49 PM
for Mark J. Goldberger, MD MPH

US006265536B1

(12) **United States Patent**
Ohki et al.

(10) **Patent No.: US 6,265,536 B1**
(45) **Date of Patent: Jul. 24, 2001**

(54) **CYCLIC HEXAPEPTIDES HAVING ANTIBIOTIC ACTIVITY**

(75) Inventors: **Hidenori Ohki**, Takarazuka; **Masaki Tomishima**, Minoo; **Akira Yamada**, Fujiidera; **Hisashi Takasugi**, Sakai, all of (JP)

(73) Assignee: **Fujisawa Pharmaceutical Co., Ltd.**, Osaka (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/248,267**

(22) Filed: **Feb. 11, 1999**

Related U.S. Application Data

(62) Division of application No. 08/809,723, filed on May 21, 1997.

(30) **Foreign Application Priority Data**

Oct. 7, 1994 (GB) 9420425
Apr. 28, 1995 (GB) 9508745

(51) **Int. Cl.**[7] **A61K 38/00**; A61K 38/12
(52) **U.S. Cl.** **530/317**; 514/9; 514/11
(58) **Field of Search** 530/317; 514/11, 514/9

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,376,634 12/1994 Iwamoto et al. .

FOREIGN PATENT DOCUMENTS

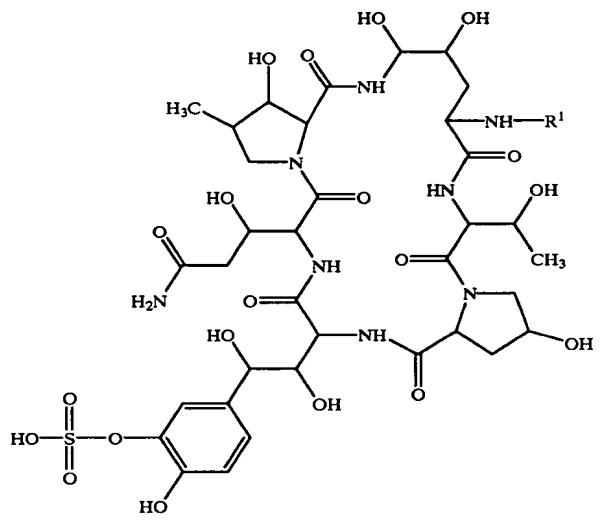
04 62531 12/1991 (EP) .

Primary Examiner—Avis M. Davenport
(74) *Attorney, Agent, or Firm*—Oblon, Spivak, McClelland, Maier & Neustadt, P.C.

(57) **ABSTRACT**

This invention relates to new polypeptide compounds represented by the following formula (I):

[I](SEQ ID NO:2)



wherein

R^1 is as defined in the description and pharmaceutically acceptable salt thereof which have antimicrobial activities (especially, antifungal activities), inhibitory activity on β-1,3-glucan synthase, to process for preparation thereof, to a pharmaceutical composition comprising the same, and to a method for the prophylactic and/or therapeutic treatment of infectious diseases including *Pneumocystis carinii* infection (e.g. *Pneumocystis carinii* pneumonia) in a human being or an animal.

17 Claims, No Drawings

CYCLIC HEXAPEPTIDES HAVING ANTIBIOTIC ACTIVITY

This application is a divisional application of Ser. No. 08/809,723 filed May 21, 1997.

TECHNICAL FIELD

The present invention relates to new polypeptide compound and a pharmaceutically acceptable salt thereof which are useful as a medicament.

BACKGROUND ART

In U.S. Pat. No. 5,376,634, there are disclosed the polypeptides compound and a pharmaceutically acceptable salt thereof, which have antimicrobial activities (especially antifungal activity).

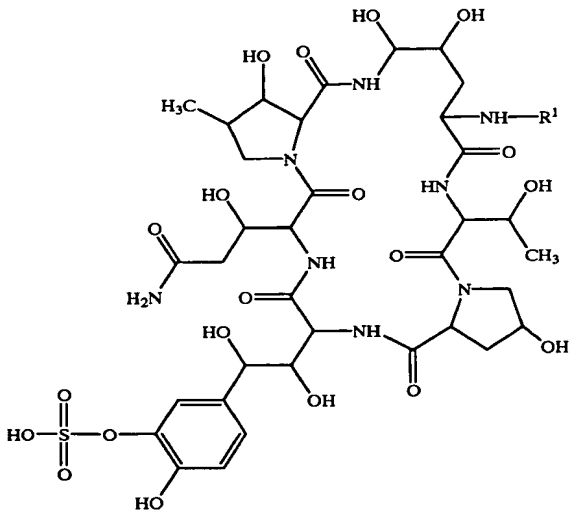
DISCLOSURE OF INVENTION

The present invention relates to new polypeptide compound and a pharmaceutically acceptable salt thereof.

More particularly, it relates to new polypeptide compound and a pharmaceutically acceptable salt thereof, which have antimicrobial activities [especially, antifungal activities, in which the fungi may include Aspergillus, Cryptococcus, Candida, Mucor, Actinomyces, Histoplasma, Dermatophyte, Malassezia, Fusarium and the like.], inhibitory activity on β-1,3-glucan synthase, and further which are expected to be useful for the prophylactic and/or therapeutic treatment of *Pneumocystis carinii* infection (e.g., *Pneumocystis carinii* pneumonia) in a human being or an animal, to a process for preparation thereof, to a pharmaceutical composition comprising the same, and to a method for the prophylactic and/or therapeutic treatment of infectious diseases including *Pneumocystis carinii* infection (e.g. *Pneumocystis carinii* pneumonia) in a human being or an animal.

The object polypeptide compound used in the present invention are new and can be represented by the following general formula [I] (SEQ ID NO:1):

[I]



wherein R^1 is lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with 1,2,3,4-tetrahydroisoquinoline which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atom (s) which may have one or more suitable substituent(s);

lower alkanoyl substituted with saturated 3 to 8 membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

ar(lower)alkenoyl substituted with aryl which may have one or more suitable substituent(s);

naphthyl(lower)alkenoyl which may have one or more higher alkoxy;

lower alkynoyl which may have one or more suitable substituent(s);

(C_2–C_6)alkanoyl substituted with naphthyl having higher alkoxy;

ar(C_2–C_6)alkanoyl substituted with aryl having one or more suitable subsitutent(s), in which ar(C_2–C_6) alkanoyl may have one or more suitable substituent(s);

aroyl substituted with heterocyclic group which may have one or more suitable substituent(s), in which aroyl may have one or more suitable substituent(s);

aroyl substituted with aryl having heterocyclic(higher) alkoxy, in which heterocyclic group may have one or more suitable substituent(s);

aroyl substituted with aryl having lower alkoxy(higher) alkoxy;

aroyl substituted with aryl having lower alkenyl(lower) alkoxy;

aroyl substituted with 2 lower alkoxy;

aroyl substituted with aryl having lower alkyl;

aroyl substituted with aryl having higher alkyl;

aryloxy(lower)alkanoyl which may have one or more suitable substituent(s);

ar(lower)alkoxy(lower)alkanoyl which may have one or more suitable substituent(s);

arylamino(lower)alkanoyl which may have one or more suitable substituent(s);

lower alkanoyl substituted with pyrazolyl which has lower alkyl and aryl having higher alkoxy;

lower alkoxy(higher)alkanoyl, in which higher alkanoyl may have one or more suitable substituent(s);

aroyl substituted with aryl having heterocyclicoxy, in which heterocyclicoxy may have one or more suitable substituent(s);

aroyl substituted with cyclo(lower)alkyl having lower alkyl;

indolylcarbonyl having higher alkyl; naphthoyl having lower alkyl; naphthoyl having higher alkyl; naphthoyl having lower alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkoxy(lower) alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkoxy(lower) alkoxy;

aroyl substituted with aryl which has aryl having lower alkoxy;

aroyl substituted with aryl which has aryl having lower alkoxy(lower)alkoxy;

aroyl substituted with aryl having heterocyclicoxy (higher)alkoxy;

aroyl substituted with aryl having aryloxy(lower)alkoxy;

aroyl substituted with aryl having heterocycliccarbonyl (higher)alkoxy;

lower alkanoyl substituted with oxazolyl which has aryl having higher alkoxy;

lower alkanoyl substituted with furyl which has aryl substituted with aryl having lower alkoxy;

lower alkanoyl substituted with triazolyl which has oxo and aryl having higher alkyl;

higher alkanoyl having hydroxy;

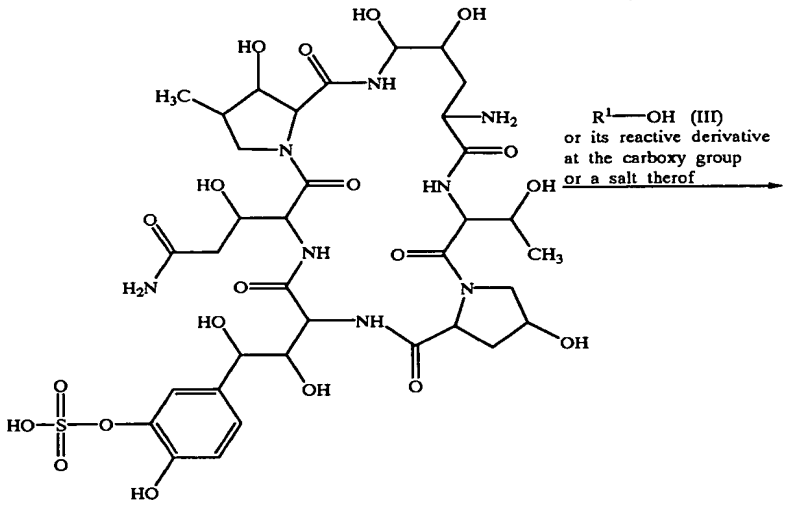
higher alkanoyl having ar(lower)alkyl and hydroxy;

3-methyl-tridecenoyl; or

(C_2–C_6)alkanoyl substituted with aryl having higher alkoxy, in which (C_2–C_6)alkanoyl may have amino or protected amino.

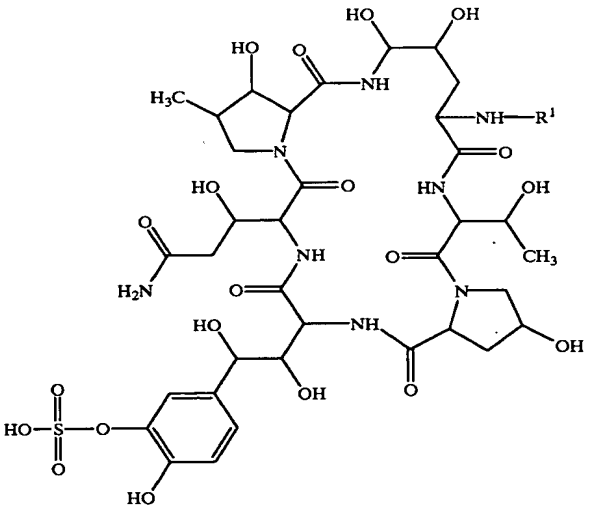
The new polypeptides compound [I] and a pharmaceutically acceptable salt thereof can be prepared by the process as illustrated in the following reaction scheme or can be prepared by elimination reaction of amino protective group in R^1.

Process 1



(II)(SEQ ID NO:1)
or its reactive derivative
at this amino group
or a salt thereof

-continued



(I)(SEQ ID NO:1)
or a salt therof

wherein R^1 is as defined above.

Suitable pharmaceutically acceptable salts of the object polypeptide compound [I] are conventional non-toxic salts and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g., sodium salt, potassium salt, etc.), in alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt, a salt with an organic base, for example, an organic amine salt (e.g., triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.); an inorganic acid addition salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.).

In the above and subsequent descriptions of the present specification, suitable examples and illustration of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is used to intend a group having 1 to 6 carbon atom(s), unless otherwise provided.

The term "higher" is used to intend a group having 7 to 20 carbon atoms, unless otherwise provided.

Suitable example of "one or more" may be the number of 1 to 6, in which the preferred one may be the number of 1 to 3.

Suitable example of "lower alkanoyl" may include straight or branched one such as formyl, acetyl, 2-methylacetyl, 2,2-dimethylacetyl, propionyl, butyryl, isobutyryl, pentanoyl, 2,2-diemthylpropionyl, hexanoyl, and the like.

Suitable example of "suitable substituent(s)" in the groups such as "lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s)", "lower alkanoyl substituted with 1,2,3,4-tetrahydroisoquinoline which may have one or more suitable substituent(s)", etc. may include lower alkoxy as mentioned below, higher alkoxy as mentioned below, lower alkyl as mentioned below, higher alkyl as mentioned below, higher alkoxy(lower)alkyl, lower alkoxycarbonyl, oxo, aryl which may have one or more lower alkoxy, aryl which may have one or more higher alkoxy, aryl which may have one or more lower alkyl, aryl which may have one or more higher alkyl, aryl substituted with aryl which may have one or more lower alkoxy, aryl substituted with aryl which may have one or more higher alkoxy, aryl substituted with aryl which may have one or more lower alkyl, aryl substituted with aryl which may have one or more higher alkyl, aroyl which may have one or more lower alkoxy, aroyl which may have one or more higher alkoxy, aroyl which may have one or more lower alkyl, aroyl which may have one or more higher alkyl, heterocyclic group which may have one or more lower alkoxy, heterocyclic group which may have one or more higher alkoxy, aryl having heterocyclic(higher)alkoxy, heterocylic group which may have aryl having higher alkoxy, heterocyclic group which may have aryl having lower alkoxy(higher)alkoxy, heterocyclic group which may have aryl having lower alkoxy, lower alkoxy(lower)alkyl, halo(lower)alkoxy, lower alkenyloxy, halo(higher)alkoxy, lower alkoxy(higher)alkoxy, aryl which may have one or more lower alkoxy(lower)alkoxy, heterocyclic group, aryl which may have one or more lower alkoxy(higher)alkoxy, aryl which may have one or more higher alkenyloxy, cyclo(lower)alkyl which may have aryl, aryl substituted with heterocyclic group which may have lower alkyl and oxo, cyclo(lower)alkyl which may have one or more lower alkyl, aryl which may have cyclo(lower)alkyl, aryl which may have heterocyclic group, and the like.

Suitable example of "lower alkoxy" may include straight or branched one such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, tert-pentyloxy, neo-pentyloxy, hexyloxy, isohexyloxy and the like,

in which the preferred one may be methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy and isohexyloxy.

Suitable example of "higher alkoxy" may include straight or branched one such as heptyloxy, octyloxy, 3,5-

dimethyloctyloxy, 3,7-dimethyloctyloxy, nonyloxy, decyloxy, undecyloxy, dodecyloxy, tridecyloxy, tetradecyloxy, hexadecyloxy, heptadecyloxy, octadecyloxy, nonadecyloxy, icosyloxy, and the like,

in which the preferred one may be (C_7–C_{14})alkoxy, and the more preferred one may be heptyloxy and octyloxy.

Suitable example of "lower alkyl" may include straight or branched one having 1 or 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl, neo-pentyl, hexyl, isohexyl and the like,

in which the preferred one may be methyl, pentyl, hexyl and isohexyl.

Suitable example of "higher alkyl" may include straight or branched one having 7 to 20 carbon atoms, such as heptyl, octyl, 3,5-dimethyloctyl, 3,7-dimethyloctyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, and the like,

in which the preferred one may be (C_7–C_{14})alkyl, and the more preferred one may be heptyl, octyl, nonyl and decyl.

Suitable example of "aryl" and "ar" moiety may include phenyl which may have lower alkyl (e.g., phenyl, mesityl, tolyl, etc.), naphthyl, anthryl, and the like,

in which the preferred one may be phenyl and naphthyl.

Suitable example of "aroyl" may include benzoyl, toluoyl, naphthoyl, anthrylcarbonyl, and the like,

in which the preferred one may be benzoyl and naphthoyl.

Suitable example of "heterocyclic group " and "heterocyclic" moiety may include

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1, 2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 to 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 to 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 to 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl, (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;

saturated 3 to 8-membered (more preferably 5 to 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 to 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 to 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;

saturated 3 to 8-membered (more preferably 5 to 6-membered) heteromonocyclic group containing an oxygen atom, for example, tetrahydrofuran, tetrahydropyran, etc.;

unsaturated 3 to 8-membered (more preferably 5 to 6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc.;

unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc.; and the like.

Suitable example of "halo" may include fluoro, chloro, bromo and iodo.

Suitable example of "lower alkenyloxy" may include vinyloxy, 1-(or 2-)propenyloxy, 1-(or 2- or 3-)butenyloxy, 1-(or 2- or 3- or 4-)pentenyloxy, 1-(or 2- or 3- or 4- or 5-)hexenyloxy, and the like, in which the preferred one may be (C_2–C_6)alkenyloxy, and the most preferred one may be 5-hexenyloxy.

Suitable example of "higher alkenyloxy" may include (C_7–C_{20})alkenyloxy, in which the preferred one may be 6-heptenyloxy and 7-octenyloxy.

Suitable example of "cyclo(lower)alkyl" may include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like, in which the preferred one may be cyclo(C_4–C_6)alkyl, and the most preferred one may be cyclohexyl.

Suitable example of "higher alkanoyl" may include heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, lauroyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, and the like, in which the preferred one may be (C_7–C_{20})alkanoyl, and the most preferred one may be hexadecanoyl.

Suitable example of "ar(lower)alkyl" may include benzyl, phenethyl, phenylpropyl, phenylbutyl, phenylpentyl, phenylhexyl, naphthylmethyl, naphthylethyl, naphthylpropyl, naphthylbutyl, naphthylpentyl, naphthylhexyl, and the like, in which the preferred one may be phenyl(C_1–C_4)alkyl, and the most preferred one may be benzyl.

Suitable example of "protected amino" may include lower or higher alkoxycarbonylamino (e.g., methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, t-pentyloxycarbonylamino, heptyloxycarbonylamino, etc.), ar(lower) alkoxycarbonylamino [e.g., phenyl(lower) alkoxycarbonylamino (e.g., benzyloxycarbonylamino, etc.), etc.], an amino group substituted with a conventional protecting group such as ar(lower)alkyl which may have suit-

able substituent(s) (e.g., benzyl, trityl, etc.) and the like, in which the preferred one may be phenyl(lower) alkoxycarbonylamino, and the most preferred one may be benzyloxycarbonylamino.

Suitable example of "lower alkanoyl" in the term of "lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be (C_1–C_4)alkanoyl, and the more preferred one may be formyl.

Suitable example of "unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom" in the term of "lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s)" may include pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl (e.g., 4H-1,2,4-triazinyl, 1H-1,2,3-triazinyl, etc.) tetrazinyl (e.g., 1,2,4,5-tetrazinyl, 1,2,3,4-tetrazinyl, etc.), and the like,

in which the preferred one may be unsaturated 6-membered heteromonocyclic group containing 1 to 3 nitrogen atom(s), and the most preferred one may be pyridyl and pyridazinyl.

Suitable example of "suitable substituent(s)" in the term of "lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic groups containing at least one nitrogen atom which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be higher alkoxy, higher alkoxy(lower)alkyl, heterocyclic group which may have aryl having higher alkoxy, aryl which may have one or more higher alkoxy, aryl substituted with aryl which may have lower alkoxy, heterocyclic group which may have aryl having lower alkoxy(higher) alkoxy, and heterocyclic group which may have aryl having lower alkoxy, and the more preferred one may be (C_7–C_{14})alkoxy, C_7–C_{14})alkoxy-(C_1–C_4)alkyl, 3 to 8-membered saturated heteromonocyclic group containing at least one nitrogen atom which may have phenyl having 1 to 3 (C_7–C_{14})alkoxy, phenyl which may have 1 to 3 (C_7–C_{14})alkoxy, phenyl substituted with phenyl which may have 1 to 3 C_3–C_6)alkoxy, 3 to 8-membered saturated heteromonocyclic group containing at least one nitrogen atom which may have phenyl having (C_1–C_4)-alkoxy(C_7–C_{14})alkoxy, and 3 to 8-membered saturated heteromonocyclic group containing at least one nitrogen atom which may have phenyl having 1 to 3 (C_3–C_6)alkoxy, and the most preferred one may be octyloxy, octyloxymethyl, piperazinyl which has phenyl having heptyloxy or octyloxy, phenyl having heptyloxy, phenyl substituted with phenyl having butoxy, piperzinyl which has phenyl having methoxyoctyloxy, and piperazinyl which has phenyl having hexyloxy.

Suitable example of "lower alkanoyl" in the term of "lower alkanoyl substituted with 1,2,3,4-tetrahydroisoquinoline which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be (C_1–C_4)-alkanoyl, and the more preferred one may be formyl.

Suitable example of "suitable substituent(s)" in the term of "lower alkanoyl substituted with 1,2,3,4-tetrahydroisoquinoline which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be lower alkoxy, higher alkoxy, lower alkyl, higher alkyl and lower alkoxycarbonyl, and the more preferred one may be (C_7–C_{14})alkoxy and (C_1–C_4)alkoxycarbonyl, and the most preferred one may be octyloxy and tert-butoxycarbonyl.

Suitable example of "lower alkanoyl" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be (C_1–C_4)alkanoyl, and the more preferred one may be formyl.

Suitable example of "unsaturated condensed heterocyclic group containing at least one oxygen atom" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have one or more suitable substituent(s)" may include unsaturated condensed heterocyclic group containing one or more oxygen atom(s) and, optionally, another hetero atom(s) except oxygen atom,

in which the preferred one may be unsaturated condensed heterocyclic group containing 1 to 3 oxygen atom(s), unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 oxygen atom(s) and 1 to 3 nitrogen atom(s), and the more preferred one may be benzo[b]furanyl, isobenzofuranyl, chromenyl, xanthenyl, benzoxazolyl, benzoxadiazolyl, dihydrooxathiinyl, phenoxathiinyl, and the like, and the most preferred one may be benzo[b]furanyl, chromenyl and benzoxazolyl.

Suitable example of "suitable substituent(s)" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, oxo, aryl which may have one or more lower alkoxy, heterocyclic group which may have one or more higher alkoxy, and aryl substituted with aryl which may have one or more lower alkyl, and the more preferred one may be (C_7–C_{14})alkoxy, (C_1–C_4)alkyl, (C_7–C_{14})alkyl, oxo, phenyl which may have 1 to 3 (C_3–C_6)alkoxy, unsaturated 6-membered heteromonochclic group containing at least one nitrogen atom which may have 1 to 3 (C_7–C_{14})alkoxy, and phenyl substituted with phenyl which may have 1 to 3 (C_3–C_6)alkyl, and the most preferred one may be octyloxy, methyl, nonyl, oxo, phenyl having hexyloxy, pyridyl having octyloxy, and phenyl substituted with phenyl having hexyl.

Suitable example of "lower alkanoyl" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be (C_1–C_4)alkanoyl, and the more preferred one may be formyl.

Suitable example of "unsaturated condensed heterocyclic group containing 1 to 3 sulfur atoms(s)" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have one or more suitable substituent(s)" may include unsaturated condensed heterocyclic group containing only 1 to 3 sulfur atom(s),

in which the preferred one may be benzothienyl and benzodithiinyl, and the most preferred one may be benzothienyl.

Suitable example of "suitable substituent(s)" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be lower alkoxy, higher alkoxy, lower alkyl and higher alkyl, and more preferred one may be (C_7–C_{14})alkoxy, and the most preferred one may be octyloxy.

Suitable example of "lower alkanoyl" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atom(s) which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be (C_1–C_4)alkanoyl, and the most preferred one may be formyl.

Suitable example of "unsaturated condensed heterocyclic group containing 2 or more nitrogen atom(s)" in the term of "lower alkanoyl substituted with unsaturated ocndensed heterocyclic group containing 2 or more nitrogen atom(s) which may have one or more suitable substituent(s)" may include 1H-indazolyl, purinyl, phthalazinyl, benzoimidazolyl, naphthyridinyl, quinoxalinyl, quinazolyl, cinnolinyl, peteridinyl, and the like,

in which the most preferred one may be benzoimidazolyl.

Suitable example of "suitable substituent(s)" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atom(s) which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, aryl which may have one or more lower alkoxy and aryl which may have one or more higher alkoxy, and the more preferred one may be (C_7–C_{14})alkyl and phenyl which may have 1 to 3 (C_1–C_6)alkoxy, and the most preferred one may be nonyl and phenyl which may have hexyloxy.

Suitable example of "lower alkanoyl" in the term of "lower alkanoyl substituted with saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be (C_1–C_4)alkanoyl, and the more preferred one may be formyl.

Suitable example of "saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom" in the term of "lower alkanoyl substituted with saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s)" may include pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl, and the like,

in which the preferred one may be piperidyl and piperazinyl.

Suitable example of "suitable substituent(s)" in the term of "lower alkanoyl substituted with saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s)" may include lower alkoxy, higher alkoxy, higher alkoxy(lower)alkyl, lower alkyl, higher alkyl, oxo, aryl which may have one or more lower alkoxy, aryl which may have one or more higher alkoxy, aryl which may have one or more lower alkyl, aryl which may have one or more higher alkyl, aroyl which may have one or more lower alkoxy, aroyl which may have one or more higher alkoxy, aroyl which may have one or more lower alkyl, aroyl which may have one or more hgiher alkyl, and the like,

in which the preferred one may be aryl which may have one or more lower alkoxy, aryl which may have one or more higher alkoxy, aroyl which may have one or more lower alkoxy and aroyl which may have one or more higher alkoxy, and the more preferred one may be aryl which may have 1 to 3 higher alkoxy and aroyl which may have 1 to 3 higher alkoxy, and the much more preferred one may be phenyl which may have 1 to 3 (C_7–C_{14})alkoxy and naphthoyl which may have 1 to 3 (C_7–C_{14})alkoxy, and the most preferred one may be phenyl which may have octyloxy and naphthoyl which may have heptyloxy.

Suitable example of "ar(lower)alkenoyl" in the term of "ar(lower)alkenoyl substituted with aryl which may have one or more suitable substituent(s)" may include phenyl (lower)alkenoyl (e.g., 3-phenylacryloyl, (2- or 3- or 4-)phenyl-(2- or 3-)butenoyl, 3-phenylmethacryloyl, (2- or 3- or 4- or 5-)phenyl-(2- or 3- or 4-)pentanoyl, (2- or 3- or 4- or 5- or 6-)phenyl-(2- or 3- or 4- or 5-)-hexanoyl, etc.), naphthyl(lower)alkenoyl (e.g., 3-naphthylacryloyl, (2- or 3- or 4-)naphthyl-(2- or 3-)butenoyl, (2- or 3- or 4- or 5-)naphthyl-(2- or 3- or 4-)pentanoyl, (2- or 3- or 4- or 5- or 6-)naphthyl-(2- or 3- or 4- or 5-)hexanoyl, etc.), and the like,

in which the preferred one may be 3-phenylacryloyl and 3-methyl-3-phenylacryloyl.

Suitable example of "suitable substituent(s)" in the term of "ar(lower)alkenoyl substituted with aryl which may have one or more suitable substitutent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be lower alkoxy, lower alkyl, higher alkyl, lower alkoxy(lower)alkyl, halo(lower)alkoxy, lower alkenyloxy, halo(higher)alkoxy, and lower alkoxy(higher)alkoxy and the much more preferred one may be (C_1–C_6)alkoxy, (C_1–C_6)alkyl, (C_7–C_{14})alkyl, (C_1–C_4)alkoxy(C_3–C_6)alkyl, halo(C_3–C_6)alkoxy, (C_3–C_6)alkenyloxy, halo(C_7–C_{14})alkoxy, and (C_1–C_4)alkoxy(C_7–C_{14})alkoxy and the most preferred one may be pentyloxy, heptyl, pentyl, methoxyhexyl, fluorohexyloxy, isohexyloxy, 5-hexenyloxy, haloheptyloxy, methoxyheptyloxy, methoxyoctyloxy, and butyloxy.

Suitable example of "naphthyl(lower)alkenoyl" in the term of "naphthyl(lower)alkenoyl which may have one or more higher alkoxy" may include 3-naphthylacryloyl, (2- or 3- or 4-)naphthyl-(2- or 3-)butenoyl, (2- or 3- or 4- or 5-)naphthyl-(2- or 3- or 4-)pentanoyl, (2- or 3- or 4- or 5- or 6-)naphthyl-(2- or 3- or 4- or 5-)hexanoyl, and the like,

in which the preferred one may be 3-naphthylacryloyl.

Suitable example of "lower alkynoyl" in the term of "lower alkynoyl which may have one or more suitable substituent(s)" may include 2-propynoyl, (2- or 3-)butynoyl, (2- or 3- or 4-)pentynoyl, (2- or 3- or 4- or 5-)hexynoyl, and the like,

in which the preferred one may be 2-propynoyl.

Suitable example of "suitable substituent(s)" in the term of "lower alkynoyl which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be aryl which may have one or more lower alkoxy, aryl which may have one or more higher alkoxy, aryl substituted with aryl which may have one or more lower alkyl and aryl substituted with aryl which may have one or more higher alkyl, and the more preferred one may be aryl substituted with aryl which may have 1 to 3 lower alkyl and aryl which may have 1 to 3 higher alkoxy, and the much more

preferred one may be phenyl substituted with phenyl which may have 1 to 3 (C_1–C_6)alkyl and phenyl which may have 1 to 3 (C_7–C_{14})alkoxy, and the most preferred one may be phenyl substituted with phenyl which may have pentyl and naphthyl which may have heptyloxy.

Suitable example of "ar(C_2–C_6)alkanoyl" in the term of "ar(C_2–C_6)alkanoyl substituted with aryl having one or more suitable substituent(s), in which ar(C_2–C_6)alkanoyl may have one or more suitable substituent(s)" may include phenyl(C_2–C_6)alkanoyl [e.g., phenylacetyl, (2- or 3-)-phenylpropanoyl, (2- or 3- or 4-)phenylbutanoyl, (2- or 3- or 4- or 5-)phenylpentanoyl, (2- or 3- or 4- or 5- or 6-)-phenylhexanoyl, etc.], naphthyl(C_2–C_6)alkanoyl [e.g. naphthylacetyl, (2- or 3-naphthylpropanoyl, (2- or 3- or 4-)naphthylbutanoyl, (2- or 3- or 4- or 5-)-naphthylpentanoyl, (2- or 3- or 4- or 5- or 6-)-naphthylhexanoyl, etc.], and the like,

in which the preferred one may be 2-phenylacetyl and 3-phenylpropanoyl.

Suitable example of "suitable substituent(s)" in the term of "ar(C_2–C_6)alkanoyl substituted with aryl having one or more suitable substituent(s), in which ar(C_2–C_6)-alkanoyl may have one or more suitable substituent(s)" may include lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, oxo, aryl having one or more lower alkoxy, aryl having one or more higher alkoxy, aryl having one or more lower alkyl, aryl having one or more higher alkyl, aryl substituted with aryl having one or more lower alkoxy, aryl substituted with aryl having one or more higher alkoxy, aryl substituted with aryl having one or more lower alkyl, aryl substituted with aryl having one or more higher alkyl, aryl having one or more lower alkoxy(lower) alkoxy and the like,

in which the preferred one may be lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, and phenyl having 1 to 3 lower alkoxy(lower)alkoxy and the much more preferred one may be (C_1–C_6)alkoxy, (C_1–C_6)alkyl, (C_7–C_{14})alkyl and phenyl having (C_1–C_4)alkoxy (C_3–C_6)alkoxy and the most preferred one may be pentyloxy, pentyl, heptyl and phenyl having methoxy-pentyloxy.

Suitable example of "suitable substituent(s)" in the term of "in which ar(C_2–C_6)alkanoyl may have one or more suitable substituent(s)" may be hydroxy, oxo, amino and aforementioned "protected amino".

Suitable example of "(C_2–C_6)alkanoyl" in the term of "(C_2–C_6)alkanoyl substituted with naphthyl having higher alkoxy" may include acetyl, propanoyl, butanoyl, pentanoyl, hexanoyl, and the like,

in which the preferred one may be propanoyl.

Suitable example of "higher alkoxy" in the term of "(C_2–C_6)alkanoyl substituted with naphthyl having higher alkoxy" can be referred to aforementioned "higher alkoxy", in which the preferred one may be (C_7–C_{14})alkoxy, and the most preferred one may be heptyloxy.

Suitable example of "aroyl" in the term of "aroyl substitued with heterocyclic group which may have one or more suitable substituent(s), in which aroyl may have one or more suitable substituent(s)" may include benzoyl, toluoyl, naphthoyl, and the like,

in which the preferred one may be benzoyl.

Suitable example of "heterocyclic group" in the term of "aroyl substituted with heterocyclic group which may have one or more suitable substituent(s), in which aroyl may have one or more suitable substituents(s)" may include unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1, 2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) hewteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2, 3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, tetrahydrofuran, tetrahydropyran, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc.;

unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc.; and the like,

in which the preferred one may be saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), unsaturated 3 to 8-membered hetero-

monocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), and

unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), and the most preferred one may be piperazinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, piperidyl, oxazolyl and pyrimidyl.

Suitable example of "suitable substituent(s)" in the term of "aroyl substituted with heterocyclic group which may have one or more suitable substituent(s), in which aroyl may have one or more suitable substituent(s)", can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be aryl which may have 1 to 3 higher alkoxy, aryl which may have 1 to 3 lower alkoxy, higher alkyl, heterocyclic group, aryl which may have 1 to 3 lower alkoxy(higher)alkoxy, aryl which may have higher alkenyloxy, heterocyclic group which may have aryl having lower alkoxy, cyclo (lower)alkyl which may have aryl, aryl which may have 1 to 3 lower alkyl, aryl which may have cyclo (lower)alkyl, aryl which may have higher alkenyloxy, aryl substituted with heterocyclic group which may have lower alkyl and oxo, cyclo(lower)alkyl which may have lower alkyl, aryl substituted with aryl which may have 1 to 3 lower alkoxy, and aryl which may have heterocyclic group, and the more preferred one may be phenyl which may have 1 to 3 (C_7–C_{14})alkoxy, phenyl which may have 1 to 3 (C_3–C_6)alkoxy, (C_7–C_{14})alkyl, saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), phenyl which may have 1 to 3 (C_1–C_4)alkoxy (C_7–C_{14})alkoxy, phenyl which may have (C_7–C_{14})alkenyloxy, saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with phenyl having (C_3–C_6)alkoxy, cyclo(C_3–C_6)alkyl which may have phenyl, phenyl which may have 1 to 3 (C_3–C_6)alkyl, phenyl which may have cyclo(C_3–C_6)alkyl, phenyl which may have (C_7–C_{14})alkenyloxy, phenyl substituted with heterocyclic group which may have (C_3–C_6) alkyl and oxo, cyclo(C_3–C_6)alkyl which may have (C_3–C_6)alkyl, phenyl substituted with phenyl which may have 1 to 3 (C_1–C_4)alkoxy, and phenyl which may have 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), and the most preferred one may be phenyl having octyloxy, phenyl having pentyloxy, phenyl having hexyloxy, heptyl, piperidyl, phenyl having isohexyloxy, phenyl having heptyloxy, phenyl having methoxyheptyloxy, phenyl having methoxyoctyloxy, phenyl having 6-heptenyloxy, piperidyl substituted with phenyl having hexyloxy, cyclohexyl having phenyl, phenyl having hexyl, phenyl having cyclohexyl, phenyl having 7-octenyloxy, phenyl substituted with triazolyl having lower alkyl and oxo, cyclohexyl having pentyl, phenyl having methoxyoctyloxy, nonyl, phenyl substituted with phenyl having propoxy, and phenyl having piperidine.

Suitable example of "suitable substituent(s)" in the term of "in which aroyl may have one or more suitable substituent (s)" may be halogen, in which the preferred one may be fluoro and chloro.

Suitable example of "aroyl" in the term of "aroyl substituted with aryl having heterocyclic(higher)alkoxy, in which heterocyclic group may have one or more suitable substituent(s)" may include benzoyl, toluoyl, naphthoyl, anthrylcarbonyl and the like,

in which the preferred one may be benzoyl.

Suitable example of "heterocyclic" moiety in the term of "aroyl substituted with aryl having heterocyclic(higher) alkoxy, in which heterocyclic group may have one or more suitable substituent(s)" can be referred to the ones as exemplified before for "heterocyclic group" in the term of "aroyl substituted with heterocyclic group which may have one or more suitable substituent(s)",

in which the preferred one may be unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) and saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), and the most preferred one may be triazolyl, tetrazolyl and morpholinyl.

Suitable example of "(higher)alkoxy" moiety in the term of "aroyl substituted with aryl having heterocyclic(higher) alkoxy, in which heterocyclic group may have one or more suitable substituent(s)" can be referred to aforementioned "higher alkoxy",

in which the preferred one may be (C_7–C_{14})alkoxy, and the most preferred one may be octyloxy.

Suitable example of "aryl" in the term of "aroyl substituted with aryl having heterocyclic(higher)alkoxy, in which heterocyclic group may have one or more suitable substituent(s)" can be referred to aforementioned "aryl",

in which the preferred one may be phenyl.

Suitable example of "suitable substituent(s)" in the term of "in which heterocyclic group may have one or more suitable substituent(s)" may be lower alkyl, in which the preferred one may be methyl.

Suitable example of "aroyl" in the term of "aroyl substituted with aryl having lower alkoxy(higher)alkoxy" may include benzoyl, toluoyl, naphthoyl, anthrylcarbonyl and the like,

in which the preferred one may be benzoyl.

Suitable example of "aryl" in the term of "aroyl substituted with aryl ahving lower alkoxy(higher)alkoxy" can be referred to aforementioned "aryl",

in which the preferred one may be phenyl.

Suitable example of "lower alkoxy(higher)akloxy" in the term of "aroyl substituted with aryl having lower alkoxy (higher)alkoxy" may be methoxyheptyloxy, methoxyoctyloxy, methoxynonyloxy, methoxydecyloxy, ethoxyheptyloxy, ethoxyoctyloxy, ethoxynonyloxy, ethoxydecyloxy, ethoxyundecyloxy, propoxyundecyloxy, butoxydodecyloxy, pentyloxytridecyloxy, hexyloxytetradecyloxy, propoxyheptyloxy, propoxyoctyloxy, propoxynonyloxy, butoxydecyloxy, or the like, in which the preferred one may be (C_1–C_6)alkoxy (C_7–C_{14})alkoxy, and the more preferred one may be methoxyoctyloxy.

Suitable example of "aroyl" in the term of "aroyl substituted with aryl having lower alkenyl(lower)alkoxy" may include benzoyl, toluoyl, naphthoyl, anthrylcarbonyl and the like,

in which the preferred one may be benzoyl.

Suitable example of "aryl" in the term of "aroyl substituted with aryl having lower alkenyl(lower)alkoxy" can be referred to aforementioned "aryl",

in which the preferred one may be phenyl.

Suitable example of "lower alkenyl(lower)alkoxy" in the term of "aroyl substituted with aryl having lower alkenyl (lower)alkoxy" may be vinylmethoxy, vinylethoxy, vinylpropoxy, vinylbutoxy, vinylpentyloxy, vinylhexyloxy, 1-(or 2-)propenylmethoxy, 1-(or 2-)propenylethoxy, 1-(or 2-)propenylpropoxy, 1-(or 2-)propenylbutoxy, 1-(or

2-)propenylpentyloxy, 1-(or 2-)propenylhexyloxy, 1-(or 2- or 3-)butenylbutoxy, 1-(or 2- or 3-)butenylhexyloxy, 1-(or 2- or 3- or 4-)pentenylpentyloxy, 1-(or 2- or 3- or 4-)pentenylhexyloxy, 1-(or 2- or 3- or 4- or 5-)hexenylbutoxy, 1-(or 2- or 3- or 4- or 5-)hexenylhexyloxy, or the like,

in which the preferred one may be (C_2–C_6)alkenyl (C_1–C_6)alkoxy, and the more preferred one may be vinylhexyloxy.

Suitable example of "aroyl substituted with 2 lower alkoxy" may include benzoyl substituted with 2 lower alkoxy and naphthoyl substituted with 2 lower alkoxy,

in which the preferred one may be benzoyl substituted with 2 (C_1–C_6)alkoxy, and the most preferred one may be benzoyl substituted with 2 pentyloxy.

Suitable example of "aroyl substituted with aryl having lower alkyl" may include benzoyl substituted with phenyl having lower alkyl, benzoyl substituted with naphthyl having lower alkyl, naphthoyl substituted with phenyl having lower alkyl, naphthoyl substituted with naphthyl having lower alkyl, and the like,

in which the preferred one may be benzoyl substituted with phenyl having (C_1–C_6)alkyl, and the most preferred one may be benzoyl substituted with phenyl having hexyl and benzoyl substituted with phenyl having pentyl.

Suitable example of "aroyl substituted with aryl having higher alkyl" may include benzoyl substituted with phenyl having higher alkyl, benzoyl substituted with naphthyl having higher alkyl, naphthoyl substituted with phenyl having higher alkyl, naphthoyl substituted with naphthyl having higher alkyl, and the like,

in which the preferred one may be benzoyl substituted with phenyl having (C_7–C_{14})alkyl, and the most preferred one may be benzoyl substituted with phenyl having heptyl.

Suitable example of "aryloxy" moiety in the term of "aryloxy(lower)alkanoyl which may have one or more suitable substituent(s)" may include phenoxy, mesityloxy, tolyloxy, naphthyloxy, anthryloxy, and the like,

in which the preferred one may be phenoxy.

Suitable example of "lower alkanoyl" moiety in the term of "aryloxy(lower)alkanoyl which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be formyl, acetyl, 2,2-dimethylacetyl, propionyl, butyryl, isobutyryl and pentanoyl, hexanoyl, and the more preferred one may be (C_1–C_6)alkanoyl, and the much more preferred one may be formyl, acetyl, propionyl and 2,2-dimethylacetyl.

Suitable example of "suitable substituent(s)" in the term of "aryloxy(lower)alkanoyl which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be (C_7–C_{14})alkoxy, and the more preferred one may be octyloxy.

Suitable example of "ar(lower)alkoxy" moiety in the term of "ar(lower)alkoxy(lower)alkanoyl which may have one or more suitable substituent(s)" may include phenyl(lower)alkoxy [e.g., phenylmethoxy, (1- or 2-)phenylethoxy, phenylpropoxy, 2-phenyl-1-methylpropoxy, 3-phenyl-2,2-dimethylpropoxy, (1- or 2- or 3- or 4-)phenylbutoxy, (1- or 2- or 3 - or 4- or 5-)phenylpentyloxy, (1- or 2- or 3- or 4- or 5- or 6-phenylhexyloxy, etc.], naphthyl(lower)alkoxy [e.g. naphthylmethoxy, (1- or 2-)naphthylethoxy, 1-naphthylpropoxy, 2-naphthyl-1-methylpropoxy, 3-naphthyl-2,2-dimetylpropoxy, (1- or 2- or 3- or 4-)naphthylbutoxy, (1- or 2- or 3- or 4- or 5-)naphthylpentyloxy, (1- or 2- or 3- or 4- or 5- or 6-)naphthylhexyloxy, etc.], and the like,

in which the preferred one may be naphthyl(C_1–C_4) alkoxy, and the more preferred one may be naphthylmethoxy.

Suitable example of "(lower)alkanoyl" moiety in the term of "ar(lower)alkoxy(lower)alkanoyl which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be (C_1–C_4)alkanoyl, and the more preferred one may be formyl.

Suitable example of "suitable substituent(s)" in the term of "ar(lower)alkoxy(lower)alkanoyl which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be lower alkoxy, higher alkoxy, lower alkyl and higher alkyl, and the more preferred one may be higher alkoxy, and the much more preferred one may be (C_7–C_{14})alkoxy, and the most preferred one may be heptyloxy.

Suitable example of "arylamino" moiety in the term of "arylamino(lower)alkanoyl which may have one or more suitable substituent(s)" may include phenylamino, mesitylamino, tolylamino, naphthylamino, anthrylamino and the like,

in which the preferred one may be phenylamino and naphthylamino.

Suitable example of "lower alkanoyl" moiety in the term of "arylamino(lower)alkanoyl which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be (C_1–C_4)alkanoyl, and the more preferred one may be formyl.

Suitable example of "suitable substituent(s)" in the term of "arylamino(lower)alkanoyl which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, aryl which may have 1 to 3 lower alkoxy and aryl which may have 1 to 3 higher alkoxy, and the more preferred one may be (C_7–C_{14})alkoxy, and phenyl which may have 1 to 3 (C_7–C_{14})alkoxy, and the most preferred one may be heptyloxy and phenyl which may have heptyloxy.

Suitable example of "lower alkanoyl" in the term of "lower alkanoyl substituted with pyrazolyl which has lower alkyl and aryl having higher alkoxy" can be referred to aforementioned "lower alkanoyl", in which the preferred one may be (C_1–C_4)alkanoyl, and the most preferred one may be formyl.

Suitable example of "lower alkyl" in the term of "lower alkanoyl substituted with pyrazolyl which has lower alkyl and aryl having higher alkoxy" can be referred to aforementioned "lower alkyl", in which the preferred one may be (C_1–C_4)alkyl, and the most preferred one may be methyl.

Suitable example of "aryl" in the term of "lower alkanoyl substituted with pyrazolyl which has lower alkyl and aryl having higher alkoxy" can be referred to aforementioned "aryl", in which the preferred one may be phenyl.

Suitable example of "higher alkoxy" in the term of "lower alkanoyl substituted with pyrazolyl which has lower alkyl and aryl having higher alkoxy" can be referred to aforementioned "higher alkoxy", in which the preferred one may be (C_7–C_{14})alkoxy, and the most preferred one may be octyloxy.

Suitable example of "lower alkoxy(higher)alkanoyl" in the term of "lower alkoxy(higher)alkanoyl, in which higher alkanoyl may have one or more suitable substituent(s)" may be (C_1–C_4)alkoxy(C_7–C_{20})alkanoyl, in which the preferred one may be methoxyoctadecanoyl.

Suitable example of "suitable substituent(s)" in the term of "lower alkoxy(higher)alkanoyl, in which higher alkanoyl may have one or more suitable substituent(s)" may be amino and aforementioned "protected amino", in which the preferred one may be amino and ar(lower) alkoxycarbonylamino, and the most preferred one may be amino and benzyloxycarbonylamino.

Suitable example of "aroyl" in the term of "aroyl substituted with aryl having heterocyclicoxy, in which heterocyclicoxy may have one or more suitable substituent(s)" can be referred to aforementioned "aroyl", in which the preferred one may be benzoyl.

Suitable example of "aryl" in the term of "aroyl substituted with aryl having heterocyclicoxy, in which heterocyclicoxy may have one or more suitable substituent(s)" can be referred to aforementioned "aryl", in which the preferred one may be phenyl.

Suitable example of "heterocyclic" moiety in the term of "aroyl substituted with aryl having heterocyclicoxy, in which heterocyclicoxy may have one or more suitable substituent(s)" can be referred to aforementioned "heterocyclic" moiety, in which the preferred one may be unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), and the most preferred one may be pyridazinyl.

Suitable example of "suitable substituent(s)" in the term of "aroyl substituted with aryl having heterocyclicoxy, in which heterocyclicoxy may have one or more suitable substituent(s)" may be aryl, in which the preferred one may be phenyl.

Suitable example of "aroyl" in the term of "aroyl substituted with cyclo(lower)alkyl having lower alkyl" can be referred to aforementioned "aroyl", in which the preferred one may be benzoyl.

Suitable example of "cyclo(lower)alkyl" in the term of "aroyl substituted with cyclo(lower)alkyl having lower alkyl" can be referred to aforementioned "cyclo(lower) alkyl", in which the preferred one may be cyclohexyl.

Suitable example of "lower alkyl" in the term of "aroyl substituted with cyclo(lower)alkyl having lower alkyl" can be referred to aforementioned "lower alkyl", in which the preferred one may be pentyl.

Suitable example of "higher alkyl" in the term of "indolylcarbonyl having higher alkyl" can be referred to aforementioned "higher alkyl" in which the preferred one may be decyl.

Suitable example of "lower alkyl" in the term of "naphthoyl having lower alkyl" can be referred to aforementioned "lower alkyl", in which the preferred one may be hexyl.

Suitable example of "higher alkyl" in the term of "naphthoyl having higher alkyl" can be referred to aforementioned "higher alkyl", in which the preferred one may be heptyl.

Suitable example of "lower alkoxy(higher)alkoxy" in the term of "naphthoyl having lower alkoxy(higher)alkoxy" may be (C_1–C_4)alkoxy(C_7–C_{14})alkoxy, in which the preferred one may be methoxyoctyloxy.

Suitable example of "aroyl" in the term of "aroyl substituted with aryl having lower alkoxy(lower)alkoxy(higher) alkoxy", "aroyl substituted with aryl having lower alkoxy (lower)alkoxy", "aroyl substituted with aryl which has aryl having lower alkoxy", "aroyl substituted with aryl which has aryl having lower alkoxy(lower)alkoxy", "aroyl substituted with aryl having heterocyclicoxy(higher)alkoxy", "aroyl substituted with aryl having aryloxy(lower)alkoxy" and "aroyl substituted with aryl having heterocycliccarbonyl (higher)alkoxy" can be referred to aforementioned "aroyl", in which the preferred one may be benzoyl.

Suitable example of "aryl" in abovementioned terms can be referred to aforementioned "aryl", in which the preferred one may be phenyl.

Suitable example of "lower alkoxy(lower)alkoxy(higher) alkoxy" in the term of "aroyl substituted with aryl having lower alkoxy(lower)alkoxy(higher)alkoxy" may be (C_1–C_4) alkoxy(C_1–C_4)alkoxy(C_7–C_{14})alkoxy, in which the preferred one may be ethoxyethoxyoctyloxy.

Suitable example of "lower alkoxy(lower)alkoxy" in the term of "aroyl substituted with aryl having lower alkoxy (lower)alkoxy" may be (C_1–C_4)alkoxy(C_3–C_6)alkoxy, in which the preferred one may be propoxyhexyloxy.

Suitable example of "lower alkoxy" in the term of "aroyl substituted with aryl which has phenyl having lower alkoxy" may be (C_3–C_6)alkoxy, in which the preferred one may be butoxy.

Suitable example of "lower alkoxy(lower)alkoxy" in the term of "aroyl substituted with aryl which has phenyl having lower alkoxy(lower)alkoxy" may be (C_1–C_4)alkoxy(C_3–C_6) alkoxy, in which the preferred one may be methoxypentyloxy and methoxyhexyloxy.

Suitable examples of "heterocyclic" moiety in the term of "aroyl substituted with aryl having heterocyclicoxy(higher) alkoxy" can be referred to aforementioned "heterocyclic" moiety, in which the preferred one may be saturated 3 to 8-membered heteromonocyclic group containing an oxygen atom, and the most preferred one may be tetrahydropyranyl.

Suitable examples of "higher alkoxy" moiety in the term of "aroyl substituted with aryl having heterocyclicoxy (higher)alkoxy" may be (C_7–C_{14})alkoxy, in which the preferred one may be octyloxy.

Suitable examples of "aryloxy(lower)alkoxy" in the term of "aroyl substituted with aryl having aryloxy(lower) alkoxy" may be phenoxy(C_3–C_6)alkoxy, in which the preferred one may be phenoxypentyloxy.

Suitable examples of "heterocyclic" moiety in the term of "aroyl substituted with aryl having heterocycliccarbonyl (higher)alkoxy" can be referred to aforementioned "heterocyclic" moiety, in which the preferred one may be saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), and the most preferred one may be piperidyl.

Suitable examples of "higher alkoxy" moiety in the term of "aroyl substituted with aryl having heterocycliccarbonyl (higher)alkoxy" can be referred to aforementioned "higher alkoxy", in which the preferred one may be (C_7–C_{14})alkoxy, and the most preferred one may be heptyloxy.

Suitable examples of "lower alkanoyl" in the term of "lower alkanoyl substituted with oxazolyl which has aryl having higher alkoxy" can be referred to aforementioned "lower alkanoyl", in which the preferred one may be (C_1–C_4)alkanoyl, and the most preferred one may be formyl.

Suitable examples of "aryl" in the term of "lower alkanoyl substituted with oxazolyl which has aryl having higher alkoxy" can be referred to aforementioned "aryl", in which the preferred one may be phenyl.

Suitable examples of "higher alkoxy" in the term of "lower alkanoyl substituted with oxazolyl which has aryl having higher alkoxy" can be referred to aforementioned "higher alkoxy", in which the preferred one may be (C_7–C_{14})alkoxy, and the most preferred one may be octyloxy.

Suitable examples of "lower alkanoyl" in the term of "lower alkanoyl substituted with furyl which has aryl substituted with aryl having lower alkoxy" can be referred to aforementioned "lower alkanoyl", in which the preferred one may be (C_1–C_4)alkanoyl, and the most preferred one may be formyl.

Suitable examples of "aryl" in the term of "lower alkanoyl substituted with furyl which has aryl substituted with aryl having lower alkoxy" can be referred to aforementioned "aryl", in which the preferred one may be phenyl.

Suitable examples of "lower alkoxy" in the term of "lower alkanoyl substituted with furyl which has aryl substituted with aryl having lower alkoxy" can be referred to aforementioned "lower alkoxy", in which the preferred one may be (C_1–C_4)alkoxy, and the most preferred one may be butoxy.

Suitable examples of "lower alkanoyl" in the term of "lower alkanoyl substituted with triazolyl which has oxo and aryl having higher alkyl" can be referred to aforementioned "lower alkanoyl", in which the preferred one may be (C_1–C_4)alkanoyl, and the most preferred one may be formyl.

Suitable examples of "higher alkyl" in the term of "lower alkanoyl substituted with triazolyl which has oxo and aryl having higher alkyl" can be referred to aforementioned "higher alkyl", in which the preferred one may be (C_7–C_{14}) alkyl, and the most preferred one may be octyl.

Suitable examples of "aryl" in the term of "lower alkanoyl substituted with triazolyl which has oxo and aryl having higher alkyl" can be referred to aforementioned "aryl", in which the preferred one may be phenyl.

Suitable examples of "higher alkanoyl" in the term of "higher alkanoyl having hydroxy" can be referred to aforementioned "higher alkanoyl", in which the preferred one may be (C_7–C_{20})alkanoyl, and the most preferred one may be hexadecanoyl.

Suitable examples of "higher alkanoyl" in the term of "higher alkanoyl having ar(lower)alkyl and hydroxy" can be referred to aforementioned "higher alkanoyl", in which the preferred one may be (C_7–C_{20})alkanoyl, and the most preferred one may be hexadecanoyl.

Suitable examples of "ar(lower)alkyl" in the term of "higher alkanoyl having ar(lower)alkyl and hydroxy" can be referred to aforementioned "ar(lower)alkyl", in which the preferred one may be phenyl(C_1–C_4)alkyl, and the most preferred one may be benzyl.

Suitable examples of "(C_2–C_6)alkanoyl" in the terms of "(C_2–C_6)alkanoyl substituted with aryl having higher alkoxy, in which (C_2–C_6)alkanoyl may have amino or protected amino" may include acetyl, propanoyl, butanoyl, pentanoyl, hexanoyl, and the like, in which the preferred one may be acetyl and propanoyl.

Suitable examples of "aryl" in the term of "(C_2–C_6) alkanoyl substituted with aryl having higher alkoxy, in which (C_2–C_6)alkanoyl may have amino or protected amino" can be referred to aforementioned "aryl", in which the preferred one may be phenyl.

Suitable examples of "higher alkoxy" in the term of "(C_2–C_6)alkanoyl substituted with aryl having higher alkoxy, in which (C_2–C_6)alkanoyl may have amino or protected amino" can be referred to aforementioned "higher alkoxy", in which the preferred one may be (C_7–C_{14})alkoxy, and the most preferred one may be octyloxy.

Suitable examples of "protected amino" in the term of "(C_2–C_6)alkanoyl substituted with aryl having higher alkoxy, in which (C_2–C_6)alkanoyl may have amino or protected amino" can be referred to aforementioned "protected amino", in which the preferred one may be ar(lower) alkoxycarbonylamino, and the most preferred one may be benzyloxycarbonylamino.

The process for preparing the object polypeptide compound [I] or a salt thereof of the present invention are explained in detail in the following.

Process 1

The object polypeptide compound [I] or a salt thereof can be prepared by reacting the compound [II] or its reactive derivative at the amino group or a salt thereof with the compound [III] or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative at the carboxy group of the compound [III] may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g., methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g., acetic acid, propionic acid, butyric acid, isobutyric acid, pivaric acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.]; or aromatic carboxylic acid [e.g., benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole, tetrazole or 1-hydroxy-1H-benzotriazole; or an activated ester [e.g., cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_{2N}^{+}$=CH—] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the mind of the compound [III] to be used.

Suitable salts of the compound [III] and its reactive derivative can be referred to the ones as exemplified for the object polypeptide compound [I].

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound [III] is sued in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)cabodiimide, N,N-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-2-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phos-

phorus oxychloride (phosphoryl chloride); phosphorus tirchloride; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g., ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl) isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorous oxychloride, methanesulfonyl chloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal carbonate, alkali metal bicarbonate, tri(lower)alkylamine, pyridine, di(lower)alkylaminopyridine (e.g., 4-dimethylaminopyridine, etc.), N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

The starting compound [II] is a known compound. It can be prepared by fermentation and synthetic processes disclosed in EP 0462531 A2.

A culture of Coleophoma sp. F-11899, which is used in said fermentation process, has been deposited with National Institute of Bioscience and Human-Technology Agency of Industrial Science and Technology (former name: Fermentation Research Institute Agency of Industrial Science and Technology) (1–3, Higashi 1-chome, Tsukubashi, IBARAKI 305, JAPAN) on Oct. 26, 1989 under the number of FERM BP-2635.

The compounds obtained by the above Process 1 can be isolated and purified by a conventional method such as pulverization, recrystallization, column-chromatography, high-performance liquid chromatography (HPLC), reprecipitation, or the like.

The compounds obtained by the above Process 1 may be obtained as its hydrate, and its hydrate is included within the scope of this invention.

It is to be noted that each of the object compound (I) may include one or more stereoisomer such as optical isomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s) and all such isomers and mixture thereof are included within the scope of this invention.

Biological Property of the Polypeptide Compound [I] of the Present Invention

In order to show the usefulness of the polypeptide compound [I] of the present invention, the biological data of the representative compound is explained in the following.

Test 1

(Antimicrobial activity):

In vitro antimicrobial activity of the compound of Example 17 disclosed later was determined by the two-fold agar-plate dilution method as described below.

Test Method

One loopful of an overnight culture of each test microorganism in Sabouraud broth containing 2% Glucose (10^5 viable cells per ml) was streaked on yeast nitrogen base dextrose agar (YNBDA) containing graded concentrations of the object polypeptide compound [I], and the minimal inhibitory concentration (MIC) was expressed in terms of μg/ml after incubation at 30° C. for 24 hours.

Test Result

Test organism	MIC (μg/ml) Test compound The compound of Example 17
candida albicans FP-633	0.2

From the test result, it is realized that the object polypeptide compound [I] of the present invention has an antimicrobial activity (especially, antifungal activity).

The pharmaceutical composition of the present invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid from, which contains the object polypeptide compound (I) or a pharmaceutically acceptable salt thereof, as an active ingredient in admixture with an organic or inorganic carrier or excipient which is suitable for rectal; pulmonary (nasal or buccal inhalation); ocular; external (topical); oral administration; parenteral (including subcutaneous, intravenous and intramuscular) administrations; insufflation (including aerosols from metered dose inhalator); nebulizer; or dry powder inhalator.

The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers in a solid form such as granules, tablets, dragees, pellets, troches, capsules, or suppositories; creams, ointments; aerosols; powders for insufflation; in a liquid form such as solutions, emulsions, or suspensions for injection; ingestion; eye drops; and any other form suitable for use. And, if necessary, there may be included in the above preparation auxiliary substance such as stabilizing, thickening, wetting, emulsifying and coloring agents; perfumes or buffer; or any other commonly may be used as additives.

The object polypeptide compound [I] or a pharmaceutically acceptable salt thereof is/are included in the pharmaceutical composition in an amount sufficient to produce the desired antimicrobial effect upon the process or condition or diseases.

For applying the composition to human, it is preferable to apply it by intravenous, intramuscular, pulmonary, oral administration, or insufflation. While the dosage of therapeutically effective amount of the object polypeptide compound [I] varies from and also depends upon the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.01–20 mg of the object polypeptide compound [I] per kg weight of human being in the case of intramuscular administration, a daily dose of 0.1–20 mg of the object polypeptide compound [I] per kg weight of human being, in case of oral administration, a daily dose of 0.5–50 mg of the object polypeptide compound [I] per kg weight of human being is generally given for treating or preventing infectious diseases.

Especially in case of the treatment of prevention of *Pneumocystis carinii* infection, the followings are to be noted.

For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized as powders which may be formulated and the powder compositions may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation aerosol, which may be formulated

as a suspension or solution of compound in suitable propellants such as fluorocarbons or hydrocarbons.

Because of desirability to directly treat lung and bronchi, aerosol administration is a preferred method of administration. Insufflation is also a desirable method, especially where infection may have spread to ears and other body cavities.

Alternatively, parenteral administration may be employed using drip intravenous administration.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

To a suspension of 1-(4-Hydroxyphenyl)-4-tert-butoxycarbonylpiperazine (3 g) and potassium carbonate (0.82 g) in N,N-dimethylformamide (15 ml) was added octyl bromide (1.87 ml). The mixture was stirred for 10 hours at 70° C. The reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel, and eluted with (hexane:ethyl acetate=9:1). The fractions containing the object compound were combined, and evaporated under reduced pressure to give 1-(4-n-Octyloxphenyl)-4-tert-butoxycarbonylpiperazine (2.71 g).

IR (KBr): 1687, 1513, 1241 cm^{-1}

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.2Hz), 1.2–1.4 (10H, m), 1.48 (9H, s), 1.65–1.85 (2H, m), 3.00 (4H, t, J=5.2Hz), 3.57 (4H, t, J=5.2Hz), 3.90 (2H, t, J=6.5Hz), 6.83 (2H, dd, J=6.4 and 2.1Hz), 6.89 (2H, dd, J=6.4 and 2.1Hz)

Preparation 2

A solution of 1-(4-n-Octyloxyphenyl)-4-tert-butoxycarbonylpiperazine (2.61 g) in trifluoroacetic acid (20 ml) was stirred for 4 hours at ambient temperature. The reaction mixture was evaporated under reduced pressure, and to the residue was added a mixture of 1N NaOH aqueous solution and ethyl acetate. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 1-(4-n-Octyloxyphenyl)piperazine (0.86 g).

IR (KBr): 2923, 1513, 1259, 831 cm^{-1}

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.4Hz), 1.2–1.53 (10H, m), 1.65–1.85 (2H, m), 3.03 (4H, s), 3.90 (2H, t, J=6.5 Hz), 6.83 (2H, dd, J=6.4 and 2.9 Hz), 6.90 (2H, dd, J=6.4 and 2.9 Hz)

APCI-MASS: m/z=291 (M^++1)

Preparation 3

To a suspension of 1-(4-n-Octyloxyphenyl)piperazine (1 g) and potassium carbonate (0.476 g) in N,N-dimethylformamide (1 ml) was added p-fluorobenzonitrile (0.347 g), and stirred for 5 hours at 160° C. The reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 4-[4-(4-n-Octyloxyphenyl)piperazin-1-yl]benzonitrile (0.93 g).

IR (KBr): 2848, 2217, 1604, 1511, 1241 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.8 Hz), 1.2–1.53 (10H, m), 1.65–1.85 (2H, m), 3.20 (4H, t J=5.4 Hz), 3.48 (4H, t, J=5.4 Hz), 3.91 (2H, t J=6.5 Hz), 6.8–7.0 (6H, m), 7.52 (2H, d, J=8.9 Hz)

APCI-MASS: m/z=392 (M^++1)

Preparation 4

A mixture of 2,4-Dihydroxybenzaldehyde (5.52 g), potassium carbonate (6.08 g) and octyl bromide (7.73 g) in acetonitrile (55 ml) was stirred for 16 hours at 60° C. The solvent of reaction mixture was removed under reduced pressure, and the residue was dissolved in ethyl acetate, and washed with water and brine. The separated organic layer was dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel and eluted with (hexane:ethyl acetate=9:1) to give 2-Hydroxy-4-octyloxybenzaldehyde (6.73 g).

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=8.8 Hz), 1.2–1.5 (10H, m), 1.8–2.0 (2H, m), 4.0–4.2 (2H, m), 6.42 (1H, s), 6.52 (1H, d, J=8.7 Hz), 7.79 (1H, d, J=8.7 Hz), 10.33 (1H, s)

APCI-MASS: m/z=257 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 4.

Preparation 5

Methyl 3,4-dipentyloxybenzoate

NMR ($CDCl_3$, δ): 0.93 (6H, t, J=6.0 and 9.0 Hz), 1.3–2.0 (12H, m), 3.88 (3H, s), 4.04 (4H, m), 6.86 (1H, d, J=8.4 Hz), 7.53 (1H, d, J=2.0 Hz), 7.63 (1H, d, J=8.4 and 2.0 Hz)

APCI-MASS: m/z=309 (M^++1)

Preparation 6

A mixture of 4-bromo-4'-pentylbiphenyl (5.04 g), trimethylsilyacetylene (2.4 ml), tetrakis(triphenylphosphine) palladium (0.96 g), triphenylphosphine (0.22 g) and cuprous iodide (95 mg) in piperidine (10 ml) was heated for an hour under atmospheric pressure of nitrogen at 90° C. The reaction mixture was poured into a mixture of cold water and ethyl acetate, and adjusted to about pH 1 with 6N hydrochloric acid. The separated organic layer was washed with water and brine, and dried over magnesium sulfate. The magnesium sulfate was filtered of, and the filtrate was evaporated under reduced pressure to give crude 2-[4-(4-pentylphenyl)phenyl]-1-trimethylsilylacetylene, which was used for the next reaction without further purification. Crude mixture was dissolved in a mixture of dichloromethane (10 ml) and methanol (10 ml), and to the solution was added potassium carbonate (2.75 g) at 0° C. The mixture was allowed to warm to ambient temperature, and stirred for another 2 hours. The reaction mixture was poured into a mixture of cold water and ethyl acetate, and the resultant precipitate was filtered off. The filtrate was adjusted to about pH 7 with 1N hydrochloric acid, and washed with brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give a crude powder, which was subjected to column chromatography on silica gel (300 ml), and eluted with a mixture of (n-hexane:ethyl acetate=99:1–97:3, V/V) to give 4-(4-Pentylphenyl)phenylacetylene (2.09 g).

IR (Nujol): 3274, 1490 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.4 Hz), 1.30–1.50 (4H, m), 1.50–1.80 (2H, m), 2.64 (2H, t, J=7.6 Hz), 7.20–7.30 (2H, m), 7.45–7.60 (6H, m)

APCI-MASS: m/z=281 (M^++1+MeOH)

The following compound was obtained according to a similar manner to that of Preparation 6.

Preparation 7

6-Heptyloxynaphthalen-2-yl-acetylene

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.5 Hz), 1.20–1.60 (8H, m), 1.70–1.90 (2H, m), 3.10 (1H, s), 4.07 (2H, t, J=6.5 Hz), 7.08 (1H, d, J=2.5 Hz), 7.15 (1H, dd, J=2.5 and 8.9 Hz), 7.47 (1H, dd, J=1.6 and 8.5 Hz), 7.64 (1H, d, J=7.3 Hz), 7.68 (1H, d, J=8.5 Hz), 7.94 (1H, d, J=1.6 Hz)

APCI-MASS: m/z=267 (M^++1)

Preparation 8

To a solution of 4-(4-Pentylphenyl)phenylacetylene (2.09 g) in tetrahydrofuran (30 ml) was added dropwise a solution of lithium diisobutylamide in a mixture of tetrahydrofuran and n-hexane (1.60 M, 5.6 ml) at −75° C., and the resultant mixture was stirred for an hour at −78° C. To the mixture was added methyl chloroformate (0.72 ml), and the reaction mixture was allowed to warm to ambient temperature. The solution was diluted with ethyl acetate, and washed in turn with water and brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give a crude product, which was subjected to column chromatography on silica gel (150 ml), and eluted with a mixture of (n-hexane:ethyl acetate=100:0–9:1, V/V) to give Methyl 3-[4-(4-pentylphenyl)phenyl]propionate (2.20 g).

IR (Nujol): 2225, 1712 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.5 Hz), 1.25–1.50 (4H, m), 1.52–1.80 (2H, m), 2.64 (2H, t, J=7.6 Hz), 3.85 (3H, s), 7.20–7.35 (2H, m), 7.40–7.70 (6H, m)

APCI-MASS: m/z=307 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 8.

Preparation 9

Methyl 3-(6-heptyloxynaphthalen-2-yl)propionate

IR (Nujol): 2219, 1704, 1621 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.5 Hz), 1.20–1.60 (8H, m), 1.70–2.00 (2H, m), 3.85 (3H, s), 4.08 (2H, t, J=6.5 Hz), 7.10 (1H, d, J=2.5 Hz), 7.17 (1H, dd, J=2.5 and 8.9 Hz), 7.52 (1H, dd, J=1.6 and 8.5 Hz), 7.68 (1H, d, J=7.3 Hz), 7.72 (1H, d, J=8.5 Hz), 8.06 (1H, d, J=1.6 Hz)

APCI-MASS: m/z=325 (M^++1)

Preparation 10

A mixture of 4-bromo-4'-pentylbiphenyl (5.0 g), methyl acrylate (2.2 ml), palladium acetate (0.11 g) and tris(o-tolyl) phosphine (0.60 g) in triethylamine (16 ml) was refluxed for 15 hours under nitrogen atmosphere. The reaction mixture was poured into a mixture of cold water and ethyl acetate, and adjusted to about pH 1.5 with 6N hydrochloric acid. The separated organic layer was washed in turn with water and brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give a crude powder, which was subjected to column chromatography on silica gel (200 ml), and eluted with a mixture of (n-hexane:ethyl acetate=100:0–94:6, V/V) to give Methyl 3-[4-(4-pentylphenyl) phenyl]acrylate (4.48 g).

IR (Nujol): 1718, 1637 cm^{-1}

NMR ($CDCl_3$, δ): 0.91 (3H, t, J=6.7 Hz), 1.20–1.50 (4H, m), 1.50 . 1.80 (2H, m), 2.65 (2H, t J=7.4 Hz), 382 (3H, s), 6.47 (1H, d, J=16.0 Hz), 7.20–7.35 (2H, m), 7.45–7.68 (6H, m), 7.73 (1H, d, J=16.0 Hz)

APCI-MASS: m/z=309 (M^++1)

The following compounds (Preparations 11 to 13) were obtained according to a similar manner to that of Preparation 10.

Preparation 11

Methyl 3-(6-heptyloxynaphthalen-2-yl)acrylate

IR (Nujol): 1716, 1625, 1459 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.5 Hz), 1.20–1.65 (8H, m), 1.76–1.93 (2H, m), 3.82 (3H, s), 4.07 (2H, t, J=6.5 Hz), 6.49 (1H, d, J=16.0 Hz), 7.05–7.20 (2H, m), 7.55 –7.90 (5H, m)

APCI-MS: m/z=327 (M^++1)

Preparation 12

Methyl 3-[4-(4-heptylphenyl)phenyl]acrylate

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.5 Hz), 1.15–1.50 (8H, m), 1.50–1.75 (2H, m), 2.64 (2H, t, J=7.6 Hz), 3.81 (3H, s), 6.46 (1H, d, J=16.0 Hz), 7.26 (2H, d, J=8.2 Hz), 7.52 (2H, d, J=8.2 Hz), 7.59 (6H, s), 7.73 (1H, d, J=16.0 Hz)

APCI-MASS: m/z=337 (M^++1)

Preparation 13

Methyl 3-[4-(4-pentyloxyphenyl)phenyl]acrylate

NMR ($CDCl_3$, δ): 0.94 (3H, t, J=7.0 Hz), 1.30–1.60 (4H, m), 1.70–1.93 (2H, m), 3.82 (3H, s), 4.00 (2H, t, J=6.7 Hz), 6.45 (1H, d, J=16.0 Hz), 6.90–7.05 (2H, m), 7.48–8.65 (6H, m), 7.72 (1H, d, J=16.0 Hz)

APCI-MASS: m/z=325 (M^++1)

Preparation 14

A mixture of 6-Heptyloxynaphthalen-2-carboxylic acid (1.00 g) and thionyl chloride (5 ml) was stirredn for 18 hours at ambient temperature, and concentrated under reduced pressure to give crude 6-heptyloxy-2-naphthoyl chloride. To a mixture of ethyl isonipecotinate (605 mg), triethylamine (425 mg) and N,N-dimethylaminopyridine (10 mg) in dichloromethane (10 ml) was added crude 6-heptyloxy-2-naphthoyl chloride, and the mixture was stirred for 2 hours at ambient temperature, and diluted with dichloromethane. The mixture was washed with water, 1N hydrochloric acid and brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and filtrate was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel, and eluted with (n-hexane:ethyl acetate=3:1) to give 4-Ethoxycarbonyl-1-(6-heptyloxy-2-naphthoyl)piperidine (1.20 g).

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.6 Hz), 1.2–2.0 (19H, m), 2.5–2.7 (1H, m), 3.0–3.2 (2H, m), 4.1–4.3 (4H, m), 7.1–7.2 (2H, m), 7.44 (1H, d, J=8.4 and 1.7 Hz), 7.72 (1H, d, J=3.9 Hz), 7.77 (1H, d, J=3.9 Hz), 7.82 (1H, s)

APCI-MASS: m/z=426 (M^+30 1)

Preparation 15

To a mixture of Methyl 3,4-diaminobenzoate (1.91 g) and triethylamine (0.56 g) in N,N-dimethylformamide (20 ml) was added decanoyl chloride (2.31 g), and the mixture was stirred for an hour at 0° C. The reaction mixture was diluted with ethyl acetate, and washed with water and brine. The separated organic layer was dried over magnesium sulfate. The magnesium sulfate was filtered off, and filtrate was

evaporated under reduced pressure. The residue was dissolved in methanol (20 ml), and conc. sulfuric acid (0.05 ml) was added, and the mixture was stirred for 6 hours at 60° C. After cooling, the reaction mixture was evaporated under reduced pressure. The residue was diluted with ethyl acetate, and washed with water and brine. The separated organic layer was dried over magnesium sulfate. The magnesium sulfate was filtered off, and filtrate was evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel eluted with (n-hexane:ethyl acetate=3:1) gave 5-Methoxycarbonyl-2-nonylbenzimidazole (1.40 g).

IR (KBr pelet): 2923, 1718, 1623, 1544, 1438, 1413, 1288, 1213, 1085, 750 cm^{-1}

NMR (DMSO-d_6, δ): 0.84 (3H, t, J=6.7 Hz), 1.1–1.4 (12H, m), 1.7–1.9 (2H, m), 2.83 (2H, t, J=7.4 Hz), 7.56 (1H, d, J=8.4 Hz), 7.78 (1H, d, J=8.4 Hz), 8.07 (1H, s)

APCI-MASS: m/z=303 (M^++1)

Preparation 16

To a mixture of dimethylmalonate (4ml), 2-hydroxy-4-octyloxybenzaldehyde (2.50 g) and piperidine (0.1 ml) in methanol (10 ml) was added acetic acid (0.01 ml), and the mixture was stirred for 3 hours at 70° C. The solvents were removed under reduced pressure, and the residue was dissolved in ethyl acetate, and washed with 0.5N hydrochloric acid, water and brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and filtrate was evaporated under reduced pressure, and the precipitate was collected by filtration, and washed with n-hexane, and dried to give Methyl 7-octyloxycoumarin-3-carboxylate (0.94 g).

NMR (DMSO-d_6, δ): 0.86 (3H, m), 1.2–1.6 (10H, m), 1.7–1.8 (2H, m), 3.81 (3H, s), 4.11 (2H, t, J=7.4 Hz), 6.9–7.1 (2H, m), 7.83 (1H, d, J=9.0 Hz), 8.75 (1H, s)

APCI-MASS: m/z=333 (M^++1)

Preparation 17

To a mixture of sodium hydride (423 mg) and 4-octylphenol (2.06 g) in tetrahydrofuran (16 ml) was added dropwise ethyl 2-chloroacetoacetate at ambient temperature. The mixture was stirred for 6 hours at 70° C. under nitrogen atmosphere, and poured into saturated ammonium chloride aqueous solution. The solution was extracted with ethyl acetate, and the organic layer was washed with water and brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was added to conc. H_2SO_4 (10 ml) at 0° C., and mixture was stirred for 10 minutes. The reaction mixture was poured into ice-water, and adjusted to pH 7.0 with 1N NaOH aqueous solution, and extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was subjected to column-chromatography on silica gel, and eluted with (hexane:ethyl acetate=95:5). The fractions containing the object compound were combined, and evaporated under reduced pressure to give Ethyl 3-methyl 5-octylbenzo[b]furan-2-carboxylate (1.44 g).

IR (Neat): 2925, 2854, 1712, 1596, 1463, 1292, 1149, 1080 cm^{-1}

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.7 Hz), 1.2–1.5 (10H, m), 1.44 (3H, t, J=7.1 Hz), 1.6–1.8 (2H, m), 2.58 (3H, s), 2.71 (2H, t, J=8.0 Hz), 4.45 (2H, t, J=7.1 Hz), 7.2–7.5 (3H, m)

APCI-MASS: m/z=317 (M^++1)

Preparation 18

To a solution of Ethyl 3-amino-4-hydroxybenzoate (1.81 g) and triethylamine (1.53 ml) in dichloromethane (20 ml) was dropwise added decanoyl chloride (2.01 ml) at 0° C. The reaction mixture was stirred for 48 hours at ambient temperature, and washed with water, 0.5N hydrochloric acid, water and brine. The separated organic layer was dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. To the residue dissolved in xylene (30 ml) was added p-tolune sulfonic acid monohydrate (0.5 g), and the mixture was stirred for 4 hours at 130° C. Ethyl acetate was added to the mixture, and washed with water and brine. The separated organic layer was dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel elluted with (n-hexane:ethyl acetate=9:1, V/V) gave Ethyl 2-nonyl benzo[b]oxazole-6-carboxylate (2.36 g).

IR (KBr pelet): 2914, 1722, 1621, 1575, 1470, 1429, 1365, 1290, 1203, 1151, 1115, 1081, 1022 cm^{-1}

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.7 Hz), 1.2–1.4 (12H, m), 1.42 (3H, t, J=7.2 Hz), 1.90 (2H, m), 2.95 (2H, t, J=7.4 Hz), 4.40 (2H, q, J=7.0 Hz), 7.50 (1H, d, J=8.5 Hz), 8.06 (1H, d, J=8.5 Hz), 8.37 (1H, s)

APCI-MASS: m/z=318 (M^++1)

Preparation 19

A mixture of Methyl 3,4-diaminobenzoate (1.84 g) and 4-hexyloxy benzaldehyde (2.30 g) in nitrobenzene (40 ml) was stirred for 48 hours at 145° C. After cooling, the mixture was evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel eluted with (n-hexane:ethyl acetate=2:1) gave 5-Methoxycarbonyl-2-(4-hexyloxyphenyl)benzimidazole (1.91 g).

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=7.4 Hz), 1.2–1.9 (8H, m), 3.92 (3H, s), 3.90–4.1 (2H, m), 6.93 (2H, d, J=8.9 Hz), 7.5–7.8 (1H, br), 7.94 (1H, dd, J=8.5 and 1.5 Hz), 8.03 (1H, d, J=8.9 Hz), 8.2–8.4 (1H, br)

APCI-MASS: m/z=353 (M^++1)

Preparation 20

A mixture of Methyl 3-[4-(4-pentylphenyl)phenyl] acrylate (2.0 g) and 10% palladium on carbon (50% wet, 0.2 g) in tetrahydrofuran (20 ml) was stirred for 8 hours under atmospheric pressure of hydrogen at ambient temperature. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure to give Methyl 3-[4-(4-pentylphenyl)phenyl]propionate (1.93 g).

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.8 Hz), 1.25–1.50 (4H, m), 1.50–1.75 (2H, m), 2.55–2.75 (4H, m), 2.99 (2H, t, J=8.0 Hz), 3.68 (3H, s), 7.10–7.30 (4H, m), 7.40–7.50 (4H, m)

APCI-MASS: m/z=311 (M^++1)

Preparation 21

A mixture of Methyl 3-[4-(4-pentyloxyphenyl)phenyl] acrylate (2.70 g) and platinum oxide (0.41 g) in tetrahydrofuran (40 ml) was stirred for 8 hours under 3 atom of hydrogen at ambient temperature. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure to give Methyl 3-[4-(4-pentyloxyphenyl)phenyl]propionate (2.70 g).

NMR ($CDCl_3$, δ): 0.95 (3H, t, J=7.0 Hz), 1.28–1.60 (4H, m), 1.60–1.95 (2H, m), 2.55–2.78 (2H, m), 2.98 (2H, t, J=7.8 Hz), 3.98 (2H, t, J=6.5 Hz), 6.85–7.05 (2H, m), 7.05–7.30 (2H, m), 7.40–7.55 (4H, m)

APCI-MASS: m/z=327 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 21.

Preparation 22

Methyl 3-(6-heptyloxynaphthalen-2-yl)propionate

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.5 Hz), 1.20–1.70 (8H, m), 1.70–1.93 (2H, m), 2.70 (2H, t, J=7.7 Hz), 3.07 (2H, t, J=7.7 Hz), 3.67 (3H, s), 4.05 (2H, t, J=6.5 Hz), 7.02–7.20 (2H, m), 7.20–7.38 (2H, m), 7.55 (1H, s), 7.66 (1H, dd, J=3.0 and 8.5 Hz)

APCI-MASS: m/z=329 (M^++1)

Preparation 23

To a mixture of Methyl 3-[4-(4-pentylphenyl)phenyl] acrylate (0.41 g) in tetrahydrofuran (5 ml) was added 3N NaOH aqueous solution (1.3 ml), and the resultant mixture was heated to 85° C. for 10 hours. The reaction mixture was poured into a mixture of cold water and ethyl acetate, and adjusted to about pH 2 with 6N hydrochloric acid. The separated organic layer was washed in turn with water and brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 3-[4-(4-Pentylphenyl)phenyl] acrylic acid (0.41 g).

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=7.5 Hz), 1.15–1.46 (4H, m), 1.48–1.70 (2H, m), 2.61 (2H, t, J=7.4 Hz), 6.56 (1H, d, J=16.0 Hz), 7.29 (2H, d, J=8.2 Hz), 7.60 (2H, d, J=4.0 Hz), 7.66 (2H, d, J=4.0 Hz), 7.68–7.85 (3H, m)

APCI-MASS: m/z=295 (M^++1)

The following compounds (Preparations 24 to 31) were obtained according to a similar manner to that of Preparation 23.

Preparation 24

3-[4-(4-Pentyloxyphenyl)phenyl]propionic acid

IR (Nujol): 1697, 1606, 1500 c^{-1}

NMR (DMSO-d_6, δ): 0.94 (3H, t, J=7.1 Hz), 1.25–1.60 (4H, m), 1.70–1.95 (2H, m), 2.72 (2H, t, J=7.5 Hz), 3.00 (2H, t, J=7.5 Hz), 3.99 (2H, t, J=6.5 Hz), 6.95 (2H, dd, J=2.1 and 6.7 Hz), 7.25 (2H, d, J=8.2 Hz), 7.40–7.60 (4H, m)

APCI-MASS: m/z=313 (M^++1)

Preparation 25

3-[4-(4-Heptylphenyl)phenyl]propionic acid

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.8 Hz), 1.15–1.50 (8H, m), 1.50–1.78 (2H, m), 2.65 (2H, t, J=7.6 Hz), 6.48 (1H, d, J=16.0 Hz), 7.27 (2H, d, J=8.2 Hz), 7.53 (2H, d, J=8.2 Hz), 7.63 (4H, m), 7.83 (1H, d, J=16.0 Hz)

APCI-MASS: m/z=323 (M^++1)

Preparation 26

3-[4-(4-Pentylphenyl)phenyl]propionic acid

NMR (DMSO-d_6, δ): 0.90 (3H, t, J=6.4 Hz), 1.20–1.50 (4H, m), 1.50–1.75 (2H, m), 2.64 (2H, t, J=8.0 Hz), 2.67 (2H, t, J=9.6 Hz), 3.00 (2H, t, J=8.0 Hz), 7.15–7.38 (4H, m), 7.38–7.60 (4H, m)

APCI-MASS: m/z=297 (M^++1)

Preparation 27

3-(6-Heptyloxynaphthalen-2-yl)propionic acid

NMR (DMSO-d_6, δ): 0.90 (3H, t, J=6.5 Hz), 1.20–1.65 (8H, m), 1.75–2.00 (2H, m), 2.75 (2H, t, J=7.7 Hz), 3.09 (2H, t, J=7.7 Hz), 4.06 (2H, t, J=6.5 Hz), 7.05–7.15 (2H, m), 7.50–7.73 (2H, m)

APCI-MASS: m/z=315 (M^++1)

Preparation 28

3-(6-Heptyloxynaphthalen-2-yl)acrylic acid

NMR (DMSO-d_6, δ): 0.90 (3H, t, J=6.5 Hz), 1.15–1.60 (8H, m), 1.75–1.95 (2H, m), 4.09 (2H, t, J=6.5 Hz), 6.51 (1H, d, J=16.0 Hz), 7.09–7.30 (2H, m), 7.65–8.00 (5H, m)

Preparation 29

3-[4-(4-Pentylphenyl)phenyl]propionic acid

NMR (DMSO-d_6, δ): 0.91 (3H, t, J=6.5 Hz), 1.23–1.50 (4H, m), 1.50–1.80 (2H, m), 2.65 (2H, t, J=7.6 Hz), 7.27 (2H, d, J=8.2 Hz), 7.51 (2H, d, J=8.2 Hz), 7.58–7.80 (4H, m)

APCI-MASS: m/z=325 (M^++1+MeOH)

Preparation 30

3-(6-Heptyloxynaphthalen-2-yl)propionic acid

IR (Nujol): 2645, 2198, 1670, 1627 c^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.5 Hz), 1.10–1.60 (8H, m), 1.65–1.90 (2H, m), 4.10 (2H, t, J=6.5 Hz), 7.24 (1H, dd, J=2.4 and 8.9 Hz), 7.39 (1H, d, J=2.5 Hz), 7.55 (1H, dd, J=1.6 and 8.5 Hz), 7.8–8.0 (2H, m), 8.22 (1H, d, J=1.6 Hz)

APCI-MASS: m/z=343 (M^++1+MeOH)

Preparation 31

4-[5-(4-Pentyloxyphenyl)isoxazolyl-3-yl]benzoic acid

IR (KBr): 2939, 2867, 1681, 1614, 1429, 1255, 1178, 821 c^{-1}

NMR (DMSO-d_6, δ): 0.91 (3H, t, J=7.1 Hz), 1.3–1.5 (4H, m), 1.6–1.8 (2H, m), 4.04 (2H, t, J=6.5 Hz), 7.11 (2H, d, J=8.9 Hz), 7.54 (1H, s), 7.85 (2H, d, J=8.9 Hz), 7.98 (2H, d, J=8.6 Hz), 8.11 (2H, d, J=8.6 Hz)

APCI-MASS: m/z=352 $(M+H)^+$

Preparation 32

To a solution of Ethyl 3-methyl-5-octylbenzo[b]furan-2-carboxylate (1.44 g) in ethanol (20 ml) was added 10% NaOH aqueous solution (2.2 ml), and stirred for 2 hours at ambient temperature, and evaporated under reduced pressure. The residue was adjusted to pH 3.0 with 1N hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 3-Methyl-5-octylbenzo[b]furan-2-carboxylic acid (1.00 g).

IR (KBr pelet): 2923, 1689, 1644, 1581, 1456, 1319, 1159, 933 c^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.7 Hz), 1.2–1.5 (10H, m), 1.5–1.8 (2H, m), 2.49 (3H, s), 2.69 (2H, t, J=7.9

Hz), 7.32 (1H, dd, J=8.5 and 1.7 Hz), 7.52 (1H, d, J=8.5 Hz), 7.54 (1H, d, J=1.7 Hz), 13.2–13.5 (1H, br)

APCI-MASS: m/z=289 (M^++1)

The following compounds (Preparations 33 to 39) were obtained according to a similar manner to that of Preparation 32.

Preparation 33

3,4-Dipentyloxybenzoic acid

NMR (DMSO-d_6, δ): 0.89 (6H, t, J=6.8 Hz), 1.2–1.5 (8H, m), 1.6–1.8 (4H, m), 3.9–4.1 (4H, m), 7.02 (1H, d, J=8.4 Hz), 7.43 (1H, d, J=1.7 Hz), 7.53 (1H, dd, J=8.4 and 1.7 Hz)

APCI-MASS: m/z=295 (M^++1)

Preparation 34

1-(6-Heptyloxy-2-naphthoyl)piperidine-4-carboxylic acid

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.7 Hz), 1.2–2.0 (14H, m), 2.5–2.6 (1H, m), 2.9–3.2 (2H, br), 3.25 (2H, s), 4.09 (2H, t, J=6.5 Hz), 7.20 (1H, dd, J=8.9 and 2.4 Hz), 7.36 (1H, d, J=2.3 Hz), 7.43 (1H, dd, J=8.4 and 1.5 Hz), 7.8–8.0 (3H, m), 12.30 (1H, br)

APCI-MASS: m/z=398 (M^++1)

Preparation 35

7-Octyloxycoumarin-3-carboxylic acid

IR (KBr): 1748, 1625, 1558, 1467, 1430, 1386, 1360, 1257, 1217, 1120 c^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.8 Hz), 1.2–1.5 (10H, m), 1.6–1.8 (2H, m), 4.11 (2H, t, J=6.4 Hz), 6.9–7.1 (2H, m), 7.82 (1H, d, J=8.9 Hz), 8.72 (1H, s), 12.98 (1H, br)

APCI-MASS: m/z=319 (M^++1)

Preparation 36

4-(4-Pentyloxyphenyl)cinnamic acid

IR (Nujol): 2923, 1675, 1500, 1290, 1223, 985, 821 c^{-1}

NMR (DMSO-d_6, δ): 0.90 (3H, t, J=7.0 Hz), 1.3–1.5 (4H, m), 1.6–1.8 (2H, m), 4.01 (2H, t, J=6.5 Hz), 6.54 (1H, d, J=16.0 Hz), 7.02 (2H, d, J=8.8 Hz), 7.5–7.8 (7H, m)

APCI-MASS: m/z=311 (M^++1)

Preparation 37

2-Nonylbenzoxazole-6-carboxylic acid

NMR (DMSO-d_6, δ): 0.84 (3H, t, J=6.7 Hz), 1.2–1.5 (12H, m), 1.7–1.9 (2H, m), 2.96 (2H, t, J=7.4 Hz), 7.76 (1H, d, J=8.4 Hz), 7.98 (1H, d, J=8.4 Hz), 8.19 (1H, s)

APCI-MASS: m/z=290 (M^++1)

Preparation 38

2-(4-Hexyloxyphenyl)benzimidazole-5-carboxylic acid

NMR (DMSO-d_6, δ): 0.8–1.0 (3H, m), 1.3–1.6 (6H, m), 1.7–1.8 (2H, m), 4.06 (2H, t, J=6.4 Hz), 7.12 (2H, d, J=8.8 Hz), 7.6–7.9 (2H, m), 8.1–8.2 (3H, m), 13.00 (1H, br)

APCI-MASS: m/z=339 (M^++1)

Preparation 39

2-Nonylbenzimidazole-5-carboxylic acid

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.7 Hz), 1.1–1.4 (12H, m), 2.7–2.9 (2H, m), 2.96 (2H, t, J=7.6 Hz), 3.6–5.2 (1H, br), 7.66 (1H, d, J=8.4 Hz), 7.90 (1H, d, J=8.4 Hz), 8.15 (1H, s)

APCI-MASS: m/z=289 (M^++1)

Preparation 40

A solution of 4-[4-(4-Octyloxyphenyl)piperazin-1-yl] benzonitrile (0.5 g) in 20% H_2SO_4 aqueous solution (30 ml) and acetic acid (20 ml) was refluxed for 9 hours. The reaction mixture was pulverized with water. The precipitate was collected by filtration, and added to a mixture of water, tetrahydrofuran and ethyl acetate, and adjusted to pH 2.5 with 1N NaOH aqueous solution. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 4-[4-(4-Octyloxyphenyl)piperazin-1-yl]benzoic acid (388 mg).

IR (KBr): 2929, 1664, 1600, 1510, 1240 c^{-1} .

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.6 Hz), 1.2–1.5 (10H, m), 1.5–1.8 (2H, m), 3.13 (4H, t, J=5.3 Hz), 3.44 (4H, t, J=5.3 Hz), 3.88 (2H, t, J=6.5 Hz), 6.83 (2H, d, J=9.2 Hz), 6.94 (2H, d, J=9.2 Hz), 7.02 (2H, d, J=9.0 Hz), 7.79 (2H, d, J=9.0 Hz)

APCI-MASS: m/z=411 (M^++1)

Preparation 41

To a suspension of sodium hydride (60% suspension in mineral oil) (0.296 g) in N,N-dimethylformamide (14 ml) was added 1,2,4-triazole (0.511 g) and 4-[4-(4-bromooctyloxy)phenyl]benzoic acid (1 g), and was stirred for 5 hours at 120° C. The reaction mixture was added to a mixture of water and ethyl acetate, and adjusted to pH 2.5 with conc. hydrochloric acid. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 4-[4-[8-(1,2,4-Triazol-1-yl) octyloxy]phenyl]benzoic acid (0.81 g).

IR (KBr): 2940, 1689, 1604, 1297, 1189 c^{-1}

NMR (DMSO-d_6, δ): 1.1–1.53 (8H, m), 1.6–1.9 (4H, m), 4.00 (2H, t, J=6.3 Hz), 4.16 (2H, t, J=7.0 Hz), 7.03 (2H, d, J=8.7 Hz), 7.67 (2H, d, J=8.7 Hz), 7.75 (2H, d, J=8.4 Hz), 7.95 (1H, s), 7.99 (2H, d, J=8.4 Hz), 8.51 (1H, s), 12.9 (1H, s)

APCI-MASS: m/z=394 (M^++1)

Preparation 42

A mixture of 2-Carbamoyl-5-methoxybenzo[b]thiophene (2.0 g), acetic acid (5 ml) and 48% hydrobromic acid (20 ml) was stirred for 16 hours at 110° C., and the mixture was poured into the ice-water. The resulting precipitate was collected by filtration, and dried to give 5-Hydroxybenzo [b]thiiophene-2-carboxylic acid (1.66 g).

NMR (DMSO-d_6, δ): 7.03 (1H, dd, J=8.8 and 0.6 Hz), 7.31 (1H, d, J=0.6 Hz), 7.81 (1H, d, J=8.8 Hz), 7.96 (1H, s), 9.64 (1H, s), 13.32 (1H, s)

APCI-MASS: m/z=195 (M^++1)

Preparation 43

A solution of (S)-2-Tert-butoxycarbonyl-1,2,3,4-tetrahydro-7-hydroxyisoquinoline-3-carboxylic acid (1 g) in a mixture of 10% NaOH aqueous solution (2.73 ml) and dimethylsulfoxide (11 ml) was stirred for half an hour at 80° C. Then, octyl bromide (0.589 ml) was added thereto, and stirred for 4 hours at 60° C. The reaction mixture was added to a mixture of water and ethyl acetate, and adjusted to pH 2.5 with conc. hydrochloric acid. The organic layer was taken, and dried over magnesium sulfate. The magnesium

sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give (S)-2-Tert-butoxycarbonyl-1,2,3,4-tetrahydro-7-octyloxyisoquinoline-3-carboxylic acid (1.30 g).

IR (Neat): 2929, 1743, 1704, 1164 c^{-1}

NMR (DMSO-d_6, δ): 0.89 (3H, t, J=6.1 Hz), 1.1–1.6 (10H, m), 1.41+1.51 (9H, s, cis+trans), 1.75 (2H, quint, J=6.5 Hz), 3.10 (2H, m), 3.90 (2H, t, J=3.9 Hz), 4.42 (1H, d, J=16.8 Hz), 4.65 (1H, d, J=16.8 Hz), 4.74+5.09 (1H, m, cic+trans), 6.5–6.8 (2H, m), 7.03 (1H, d, J=8.3 Hz)

APCI-MASS: m/z=306 (M^++1–Boc)

The following compounds (Preparations 44 to 45) were obtained according to a similar manner to that of Preparation 43.

Preparation 44

5-Octyloxybenzo[b]thiophene-2-carboxylic acid

IR (KBr): 1673, 1666, 1600, 1517, 1409, 1267, 1214, 1153, 865 c^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 1.2–1.5 (10H, m), 1.7–1.9 (2H, m), 4.02 (2H, t, J=6.4 Hz), 7.13 (1H, dd, J=8.9 and 0.6 Hz), 7.51 (1H, d, J=0.6 Hz), 7.90 (1H, d, J=9.0 Hz), 7.99 (1H, s)

APCI-MASS: m/z=307 (M^++1)

Preparation 45

4-[4-(4-Hexyloxyphenyl)piperazin-1-yl]benzoic acid dihydrochloride

IR (KBr): 1668, 1600, 1510, 1228 c^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.9 Hz), 1.2–1.5 (6H, m), 1.6–1.9 (2H, m), 3.0–3.2 (4H, m), 3.3–3.5 (4H, m), 3.88 (2H, t, J=6.3 Hz), (2H, d, J=9 Hz), 6.9–7.1 (4H, m), 7.79 (2H, d, J=8.8 Hz), 12.32 (1H, s)

APCI-MASS: m/z=383 ($M+H^+$)

Preparation 46

To a suspension of dimethyl terephthalate (1.94 g) and potassiuim t-butoxide (2.24 g) in tetrahydrofuran (30 ml) was added 4-pentyloxyacetophenone (1.59 g) in tetrahydrofuran (10 ml) at 70° C. dropwise. The mixture was refluxed for 30 minutes and poured into 1N HCl (50 ml). The mixture was extracted with ethyl acetate (100 ml) and the organic layer was washed with H_2O (100 ml), brine (100 ml) and evaporated under reduced pressure. The residue was triturated with acetonitrile (20 ml), collected by filtration and dried under reduced pressure to give 1-(4-Methoxycarbonylphenyl)-3-(4-pentyloxyphenyl)propane-1, 3-dione (2.41 g) as yellow solid.

IR (KBr): 3475, 2956, 2923, 1720, 1606, 1508, 1284, 1176, 1108, 769 c^{-1}

NMR (DMSO-d_6, δ): 0.95 (3H, t, J=7.0 Hz), 1.3–1.5 (4H, m), 1.7–2.0 (2H, m), 3.96 (3H, s), 4.04 (2H, t, J=6.5 Hz, 6.82 (1H, s), 6.96 (2H, d, J=8.9 Hz), 8.0–8.1 (4H, m), 8.14 (2H, m, J=8.7 Hz), 12–13 (1H, br)

APCI-MASS: m/z=369 ($M+H^+$)

Preparation 47

The solution of 1-(4-Methoxycarbonylphenyl)-3-(4-pentyloxyphenyl)propane-1,3-dione (1.00 g) and hydroxylamine hydrochloride (567 mg) in methanol (10 ml) was refluxed for 10 hours. The reaction mixture was diluted with ethyl acetate (50 ml) and washed with water (50 ml×2), brine (50 ml). The organic layer was dried over magnesium sulfate and the solvents were removed under reduced pressure. The residue was triturated with acetonitrile (10 ml), collected by filtration, and dried under reduced pressure to give Methyl 4-[5-(4-pentyloxyphenyl)isoxazol-3-yl] benzoate (0.74 g).

IR (KBr): 2942, 2873, 1716, 1616, 1508, 1280, 1108 cm^{-1}

NMR ($CDCl_3$, δ): 0.95 (3H, t, J=6.9 Hz), 1.3–1.6 (4H, m), 1.8–2.0 (2H, m), 3.95 (3H, s), 4.02 (2H, t, J=6.5 Hz), 6.74 (1H, s), 6.99 (2H, d, J=8.8 Hz), 7.76 (2H, d, J=8.8 Hz), 7.93 (2H, d, J=8.5 Hz), 8.14 (2H, d, J=8.5 Hz)

APCI-MASS: m/z=366 $(M+H)^+$

Preparation 48

A solution of 4-[4-(8-Bromooctyloxy)phenyl]benzoic acid (1 g) in a mixture of sodium methylate (28% solution in methanol) (10 ml) and N,N-dimethylformamide (5 ml) was refluxed for 5 hours. The reaction mixture was added to a mixture of water and ethyl acetate and adjusted to pH 2.0 with conc. HCl. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 4-[4-(8-Methoxyoctyloxy)phenyl]benzoic acid (0.77 g).

IR (KBr): 2935, 1685, 835, 773 cm^{-1}

NMR ($CDCl_3$, δ): 1.27–1.7 (10H, m), 1.7–1.95 (2H, m), 3.34 (3H, s), 3.38 (2H, t, J=6.4 Hz), 4.01 (2H, t, J=6.5 Hz), 6.99 (2H, d, J=8.7 Hz), 7.58 (2H, d, J=8.7 Hz), 7.66 (2H, d, J=8.4 Hz), 8.15 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=399 (M^++H–H_2O)

Preparation 49

To a suspension of 1-Hydroxybenzotriazole (0.283 g) and 6-octyloxymethylpicolinic acid (0.505 g) in dichloromethane (15 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSCD.HCl) (0.473 g), and stirred for 3 hours at ambient temperature. The reaction mixture was poured into water. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 1-(6-Octyloxymethylpicolinoyl)benzotriazole 3-oxide (737 mg).

IR (Neat): 1793, 1654, 1591, 1039 cm^{-1}

The following compounds [Preparations 50 to 66) were obtained according to a similar manner to that of Preparation 49.

Preparation 50

1-[4-(4-Octyloxyphenyl)piperazin-1-yl)benzoyl] benzotriazole 3-oxide

IR (KBr): 1783, 1600, 1511, 1232, 1184 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.6 Hz), 1.2–1.65 (10H, m), 1.65–1.9 (2H, m), 3.24 (4H, t, J=5.3 Hz), 3.62 (4H, t, J=5.3 Hz), 3.93 (2H, t, J=6.5 Hz), 6.8–7.1 (6H, m), 7.35–7.63 (3H, m), 8.0–8.25 (3H, m)

Preparation 51

1-[4-[4-[8-(1,2,4-Triazol-1-yl)octyloxy]phenyl] benzoyl]benzotriazole 3-oxide

IR (KBr): 1776, 1600, 1193, 983 cm^{-1}

NMR ($CDCl_3$, δ): 1.2–2.0 (12H, m), 4.03 (2H, t, J=6.4 Hz), 4.18 (2H, t, J=7.1 Hz), 7.02 (2H, d, J=8.7 Hz), 7.4–7.63 (3H, m), 7.63 (2H, d, J=8.7 Hz), 7.79 (2H, d, J=8.3 Hz), 7.95 (1H, s), 8.06 (1H, s), 8.12 (1H, d, J=7.7 Hz), 8.32 (2H, d, J=8.3 Hz)

APCI-MASS: m/z=511 (M^++1)

Preparation 52

1-[2-Methyl-2-(4-octyloxyphenoxy)propionyl] benzotriazole 3-oxide

IR (Neat): 2927, 1810, 1504, 1047 cm^{-1}

Preparation 53

1-[2(4-Octyloxyphenoxy)propionyl]benzotriazole 3-oxide

IR (KBr): 2954, 1812, 1513, 1232 cm^{-1}

Preparation 54

1-[(S)-2-tert-Butoxycarbonyl-1,2,3,4-tetrahydro-7-octyloxyisoquinolin-3-yl-carbonyl]benzotriazole 3-oxide

IR (Neat): 2929, 1816, 1739, 1704, 1392 cm^{-1}

Preparation 55

Succinimido 4(4-n-octyloxyphenyl)piperazine-1-carboxylate

IR (KBr): 2925, 1758, 1743, 1513, 1241 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.8 Hz), 1.2–1.5 (10H, m), 1.65–1.85 (2H, m), 2.83 (4H, s), 3.0–3.2 (2H, m), 3.6–3.85 (2H, m), 3.91 (2H, t, J=6.5 Hz), 6.84 (2H, dd, J=8.5 and 2.7 Hz), 6.90 (2H, dd, J=8.5 and 2.7 Hz)

APCI-MASS: m/z=432 (M^++1)

Preparation 56

(6-Heptyloxy-2-naphthyl)methylsuccinimido carbonate

IR (KBr): 1878, 1832, 1787, 1735, 1209 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.2 Hz), 1.2–1.6 (8H, m), 1.73–2.0 (2H, m), 2.83 (4H, s), 4.07 (2H, t, J=6.5 Hz), 5.44 (2H, s), 7.13 (1H, d, J=2.4 Hz), 7.17 (1H, dd, J=8.8 and 2.4 Hz), 7.44 (1H, dd, J=8.4 and 1.6 Hz), 7.67–7.85 (3H, m)

Preparation 57

1-(3,4-Dipentyloxybenzoyl)benzotriazole 3-oxide

IR (KBr): 2952, 1774, 1594, 1515, 1430, 1272, 1147, 1089 cm^{-1}

NMR ($CDCl_3$, δ): 0.9–1.1 (6H, m), 1.3–1.6 (8, m), 1.8–2.1 (4H, m), 4.0–4.2 (4H, m), 6.99 (1H, d, J=8.5 Hz), 7.4–7.6 (3H, m), 7.68 (1H, d, J=2.0 Hz), 7.92 (1H, dd, J=8.5 and 2.0 Hz), 8.10 (1H, d, J=8.5 Hz)

APCI-MASS: m/z=412 (M^++1)

Preparation 58

1-(7-Octyloxycoumarin-3-yl-carbonyl)benzotriazole 3-oxide

IR (KBr): 2925, 1754, 1716, 1610, 1548, 1282, 1199, 1172, 1139, 1064, 781, 750 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=7.8 Hz), 1.2–1.5 (10H, m), 1.6–1.8 (2H, m), 4.11 (2H, t, J=6.5 Hz), 6.9–7.1 (2H, m), 7.41 (1H, t, J=7.2 Hz), 7.54 (1H, t, J=7.2 Hz), 7.72 (1H, d, J=8.3 Hz), 7.82 (1H, d, J=8.3 Hz), 7.99 (1H, d, J=8.3 Hz), 8.72 (1H, s)

APCI-MASS: m/z=436 (M^++1)

Preparation 59

1-[4-(4-Pentyloxyphenyl)cinnamoyl]benzotriazole 3-oxide

IR (Nujol): 2854, 1778, 1708, 1620, 1597, 1494, 1459, 1434, 1377, 1350, 1250, 1188, 1138, 1086, 978 cm^{-1}

Preparation 60

1-(5-Octyloxybenzo[b]thiophen-2-yl-carbonyl)-benzotriazole 3-oxide

IR (KBr): 2950, 1776, 1517, 1342, 1211, 1151 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 1.2–1.5 (10H, m), 1.7–1.9 (2H, m), 4.01 (2H, t, J=6.4 Hz), 7.13 (1H, dd, J=8.8 and 2.4 Hz), 7.42 (1H, d, J=7.1 Hz), 7.5–7.6 (3H, m), 7.72 (1H, d, J=8.4 Hz), 7.89 (1H, d, J=8.8 Hz), 7.9–8.1 (2H, m)

APCI-MASS: m/z=424 (M^++1)

Preparation 61

1-(3-Methyl-5-octylbenzo[b]furan-2-yl-carbonyl)-benzotriazole 3-oxide

IR (KBr): 1776, 1575, 1469, 1363, 1324, 1276, 1114, 1027 cm^{-1}

NMR (CDClhd **3**, δ): 0.89 (3H, t, J=6.7 Hz), 1.2–1.5 (10H, m), 2.6–2.8 (2H, m), 2.71 (3H, s), 2.76 (2H, t, J=7.4 Hz), 7.4–7.6 (6H, m), 8.12 (1H, s)

APCI-MASS: m/z=406 (M^++1)

Preparation 62

1-(2-Nonylbenzoxazol-5-yl-carbonyl)benzotriazole 3-oxide

IR (KBr): 2980, 1783, 1623, 1573, 1276, 1151, 1091, 989 cm^{-1}

NMR (DMSO-d_6, δ): 0.84 (3H, t, J=6.8 Hz), 1.1–1.4 (12H, m), 1.81 (2H, t, J=7.2 Hz), 2.96 (3H, t, J=7.4 Hz), 7.41 (1H, t, J=7.0 Hz), 7.54 (1H, t, J=7.0 Hz), 7.74 (2H, t, J=7.0 Hz), 7.98 (2H, d, J=7.0 Hz), 8.19 (1H, s)

APCI-MASS: m/z=407 (M^++1)

Preparation 63

1-[2-(4-Hexyloxyphenyl)benzimidazol-5-yl-carbonyl]benzotriazole 3-oxide

IR (KBr): 3160, 2931, 2863, 1778, 1612, 1502, 1448, 1388, 1294, 1247, 1174, 1097, 1010, 732 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (3H, t, J=6.7 Hz), 1.2–1.5 (6H, m), 1.7–1.8 (2H, m), 4.08 (2H, t, J=6.4 Hz), 7.16 (2H, d, J=8.7 Hz), 7.6–8.4 (9H, m), 8.3–8.6 (1H, br)

APCI-MASS: m/z=456 (M^++1)

Preparation 64

1-[4-[4-(8-Methoxyoctyloxy)phenyl]benzoyl] benzotriazole-3-oxide

IR (KBr): 2931, 1793, 1770, 1600 cm^{-1}

NMR ($CDCl_3$, δ): 1.2–1.7 (10H, m), 1.7–1.93 (2H, m), 3.34 (3H, s), 3.38 (2H, t, J=6.4 Hz), 4.03 (2H, t, J=6.5 Hz), 7.03 (2H, d, J=8.8 Hz), 7.4–7.7 (3H, m), 7.63 (2H, d, J=8.8 Hz), 7.79 (2H, d, J=8.6 Hz), 8.12 (1H, d, J=8.2 Hz), 8.32 (2H, d, J=8.6 Hz)

Preparation 65

1-[4-[4-(4-Hexyloxyphenyl)piperazin-1-yl]benzoyl] benzotriazole 3-oxide

IR (KBr): 1770, 1604, 1510, 1232, 1186 cm^{-1}

NMR ($CDCl_3$, δ): 0.91 (3H, t, J=6.6 Hz), 1.2–1.6 (6H, m), 1.6–1.9 (2H, m), 3.1–3.3 (4H, m), 3.5–3.7 (4H, m), 3.93 (2H, t, J=6.5 Hz), 6.87 (2H, d, J=9.2 Hz), 6.96 (2H, d, J=9.2 Hz), 7.00 (2H, d, J=9.0 Hz), 7.3–7.7 (3H, m), 8.10 (1H, d, J=8.2 Hz), 8.15 (2H, d, J=9.0 Hz)

APCI-MASS: m/z=500 ($M+H^+$)

Preparation 66

1-[4-[5-(4-Pentyloxyphenyl)isoxazol-3-yl]benzoyl] benzotriazole 3-oxide

IR (KBr): 2950, 2837, 1774, 1616, 1508, 1452, 1251, 1006 cm^{-1}

NMR ($CDCl_3$, δ): 0.95 (3H, t, J=7.1 Hz), 1.3–1.5 (4H, m), 1.8–2.0 (2H, m), 4.04 (2H, t, J=6.5 Hz), 6.81 (1H, s), 7.0–7.1 (3H, m), 7.4–7.6 (3H, m), 7.80 (2H, d, J=8.8 Hz), 8.0–8.2 (3H, m), 8.40 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=469 $(M+H)^+$

Preparation 67

To a suspension of 1-hydroxybenzotriazole (0.20 g) and 4-(4-pentylphenyl)cinnamic acid (0.40 g) in dichloromethane (12.0 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (0.33 g) (WSCD.HCl), and the mixture was stirred for 12 hours at ambient temperature. The reaction mixture was diluted with dichloromethane, and washed with brine, and dried over magnesium sulfate. After magnesium sulfate was filtered off, evaporation of the filtrate and trituration with acetonitrile gave 1-[4-(4-Pentylphenyl)cinnamoyl]benzotriazole 3-oxide (0.24 g).

NMR ($CDCl_3$, δ): 0.91 (3H, t, J=6.6 Hz), 1.20–1.50 (4H, m), 1.50–1.75 (2H, m), 2.66 (2H, t, J=8.0 Hz), 7.20–8.25 (11H, m), 8.55 (1H, d, J=8.4 Hz)

APCI-MASS: m/z=412 (M^++1)

The following compounds (Preparations 68 to 73) were obtained according to a similar manner to that of Preparation 67.

Preparation 68

1-[3-[4-(4-Pentyloxyphenyl)phenyl]-2-propanoyl] benzotriazole 3-oxide

NMR ($CDCl_3$, δ): 0.90–1.05 (3H, m), 1.30–1.65 (4H, m), 1.70–1.95 (2H, m), 3.10–3.60 (4H, m), 3.90–4.10 (2H, m), 6.88–7.08 (2H, m), 7.20–8.50 (10H, m)

APCI-MASS: m/z=430 (M^++1)

Preparation 69

1-[4-(4-Heptylphenyl)cinnamoyl]benzotriazole 3-oxide

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.7 Hz), 1.20–1.50 (8H, m), 1.50–1.80 (2H, m), 2.66 (2H, t, J=7.6 Hz), 6.70–8.60 (12H, m)

APCI-MASS: m/z=440 (M^++1)

Preparation 70

1-[3-[4-(4-Pentylphenyl)phenyl]-2-propanoyl] benzotriazole 3-oxide

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.8 Hz), 1.20–1.50 (4H, m), 1.50–1.76 (2H, m), 2.63 (2H, t, J=7.4 Hz), 3.21 (2H, t, J=7.3 Hz), 3.51 (2H, t, J=7.3 Hz), 7.20–7.45 (4H, m), 7.45–7.50 (5H, m), 7.78 (1H, dt, J=1.0 and 7.2 Hz), 8.00 (1H, d, J=8.2 Hz), 8.42 (1H, d, J=8.4 Hz)

APCI-MASS: m/z=414 (M^++1)

Preparation 71

1-[3-(6-Heptyloxynaphthalen-2-yl)propanoyl] benzotriazole 3-oxide

NMR ($CDCl_3$, δ): 0.80–1.10 (3H, m), 1.20–1.70 (8H, m), 1.70–2.00 (2H, m), 3.10–3.70 (4H, m), 4.00–4.18 (2H, m), 6.80–8.50 (10H, m)

APCI-MASS: m/z=432 (M^++1)

Preparation 72

1-[3-(6-Heptyloxynaphthalen-2-yl)propenoyl] benzotriazole 3-oxide

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.5 Hz), 1.20–1.65 (8H, m), 1.75–1.95 (2H, m), 4.10 (2H, d, J=6.5 Hz), 6.75–8.62 (8H, m)

APCI-MASS: m/z=430 (M^++1)

Preparation 73

1-(4-Hexylphenylbenzoyl)benzotriazole 3-oxide

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=4.4 Hz), 1.2–1.5 (6H, m), 1.6–1.8 (2H, m), 2.68 (2H, t, J=8.0 Hz), 7.32 (2H, d, J=8.2 H), 7.4–7.7 (5H, m), 7.81 (2H, d, J=6.6 Hz), 8.10 (2H, d, J=8.1 Hz), 8.32 (2H, d, J=7.6 Hz)

APCI-MASS: m/z=400 (M^++1)

Preparation 74

To a solution of 4-octyloxyphenol (1 g) in dimethylformamide (10 ml) and pyridine (0.364 ml) was added N,N'-disuccinimidylcarbonate (1.16 g). The mixture was stirred for 12 hours at ambient temperature. The reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 4-Octyloxyphenylsuccinimidyl carbonate (0.59 g).

IR (KBr): 2927, 1876, 1832, 1735 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.3 Hz), 1.2–1.55 (10H, m), 1.67–1.87 (2H, m), 2.87 (4H, s), 3.94 (2H, t, J=6.5 Hz), 6.89 (2H, d, J=9.2 Hz), 7.17 (2H, d, J=9.2 Hz)

APCI-MASS: m/z=364 (M^++1)

The following compounds (Preparations 75 to 88) were obtained according to a similar manner to that of Preparation 1.

Preparation 75

Methyl 4-[4-(6-phenylpyridazin-3-yl-oxy)phenyl] benzoate

IR (KBr): 1708, 1427, 1280, 1187, 1112 cm^{-1}

NMR ($CDCl_3$, δ): 3.95 (3H, s), 7.2–7.7 (10H, m), 7.92 (1H, d, J=9.2 Hz), 8.0–8.2 (4H, m)

APCI-MASS: m/z=383 $(M+H)^+$

Preparation 76

Methyl 4-[4-(5-bromopentyloxy)phenyl]benzoate

IR (KBr): 2946, 2871, 1716, 1602, 1294, 1199, 1112, 837 cm^{-1}

NMR ($CDCl_3$, δ): 1.7–2.0 (6H, m), 3.45 (2H, t, J=6.7 Hz), 3.93 (3H, s), 4.02 (2H, t, J=6.1 Hz), 6.97 (2H, d, J=8.7 Hz), 7.56 (2H, d, J=8.7 Hz), 7.61 (2H, d, J=8.3 Hz), 8.07 (2H, d, J=8.3 Hz)

APCI-MASS: m/z=378 $(M+H)^+$

Preparation 77

Methyl 4-[4-(5-phenoxypentyloxy)phenyl]benzoate

IR (KBr): 2944, 2931, 1720, 1600, 1492, 1197, 1110 cm^{-1}

NMR ($CDCl_3$, δ): 1.6–1.8 (2H, m), 1.8–2.0 (4H, m), 3.93 (3H, s), 4.00 (2H, t, J=6.3 Hz), 4.04 (2H, t, J=6.3 Hz), 6.9–7.1 (5H, m), 7.3–7.4 (2H, m), 7.56 (2H, d, J=8.7 Hz), 7.62 (2H, d, J=8.3 Hz), 8.07 (2H, d, J=8.3 Hz)

APCI-MASS: m/z=391 $(M+H)^+$

Preparation 78

1-[2-(4-Cyclohexylphenylamino)ethyl]-2-oxazolidione hydrochloride

IR (KBr): 2923.6, 2852,2, 1747.2, 1683.6 cm^{-1}

NMR (DMSO-d_6, δ): 1.1–1.5 (6H, m), 1.6–1.9 (4H, m), 2.3–2.6 (1H, m), 3.3–3.5 (4H, m), 3.58 (2H, dd, J=9.4 and 7.4 Hz), 4.22 (2H, dd, J=9.4 and 7.4 Hz), 7.1–7.4 (4H, m)

Preparation 79

Methyl 4-[4-(8-hydroxyoctyloxy)phenyl]benzoate

IR (KBr): 3250, 2933, 2856, 1724, 1602, 1436, 1292, 1199 cm^{-1}

NMR ($CDCl_3$, δ): 1.3–1.9 (12 H, m), 3.6–3.8 (2 H, br), 3.93 (3 H, s), 4.00 (2 H, t, J=6.7 Hz), , 4.82 (1 H, s), 7.68 (2 H, d, J=8.7 Hz), 7.56 (2 H, d, J=8.7 Hz), 7.62 (2 H, d, J=8.3 Hz), 8.07 (2 H, d, J=8.3 Hz)

APCI-MASS: m/z=357 $(M+H^+)$

Preparation 80

Methyl 4-[4-(6-bromohexyloxy)phenyl]benzoate

IR (KBr): 2937,2861,1724,1602,1529,1436,1292, 1199, 1112 cm^{-1}

NMR ($CDCl_3$, δ): 1.5–2.0 (8 H, m), 3.43 (2 H, t, J=6.8 Hz), 3.93 (3 H, s), 4.02 (2 H, t, J=6.3 Hz), 6.98 (2 H, d, J=8.8 Hz), 7.56 (2 H, d, J=8.8 Hz), 7.62 (2 H, d, J=8.4 Hz), 8.07 (2 H, d, J=8.4 Hz)

APCI-MASS: m/z=391 $(M+H^+)$

Preparation 81

4-[4-(5-Bromopentyloxy)phenyl]bromobenzene

IR (KBr): 2942,2867,1604, 1515, 1477, 1286 cm^{-1}

NMR ($CDCl_3$, δ): 1.5–2.0 (6 H, m), 3.44 (2 H, t, J=6.7 Hz), 3.99 (2 H, t, J=6.2 Hz), 6.95 (2 H, d, J=8.7 Hz), 7.3–7.6 (6 H, m)

APCI-MASS: m/z=399 $(M+H^+)$

Preparation 82

8-[4-(4-Methoxycarbonylphenyl)phenoxy]octanoyl piperidine

IR (KBr): 2935, 2852, 1720, 1639, 1604, 1438, 1292 cm^{-1}

NMR ($CLCl_3$, δ): 1.3–1.9 (16 H, m) 2.34 (2 H, d, J=7.6 Hz), 3.4–3.6 (4 H, m), 3.93 (3 H, s), 3.99 (2 H, t, J=6.4 Hz), 6.97 (2 H, d, J=8.8 Hz), 7.55 (2 H, d, J=8.8 Hz), 7.61 (2 H, d, J=8.6 Hz), 8.07 (2 H, d, J=8.6 Hz)

APCI-MASS: m/z=438 $(M+H^+)$

Preparation 83

Methyl 6-[4-(4-n-heptyloxyphenyl)piperazin-1-yl] nicotinate

IR (KBr): 2933, 2859, 1726, 1608, 1513, 1430, 1280, 1245 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3 H, t, J=6.7 Hz), 1.2–1.8 (10 H, m), 3.17 (4 H, t, J=4.9 Hz), 3.8–4.0 (9 H, m), 6.65 (1 H, d, J=9.1 Hz), 6.86 (2 H, d, J=9.1 Hz), 6.96 (2 H, d, J=9.1 Hz), 8.05 (1 H, dd, J=9.1 and 2.3 Hz), 8.82 (1 H, d, J=2.3 Hz)

APCI-MASS: m/z=412 $(M+H^+)$

Preparation 84

Methyl 6-[4-[4-(8-bromooctyloxy)phenyl]piperazin-1-yl]nicotinate

Ir (KBr): 2933, 2861, 1724, 1608, 1513, 1430, 1280 cm^{-1}

NMR ($CDCl_3$, δ): 1.2–2.0 (12 H, m), 3.17 (4 H, t, J=5.0 Hz), 3.40 (2 H, t, J=6.8 Hz), 3.8–4.0 (9 H, m), 6.64 (1 H, d, J=9.0 Hz), 6.85 (2 H, d, J=9.1 Hz), 6.96 (2 H, d, J=9.1 Hz), 8.05 (1 H, dd, J=9.0 and 2.2 Hz), 8.82 (1 H, d, J=2.2 Hz)

APCI-MASS: m/z=504 $(M+H^+)$

Preparation 85

4-[4-(7-Bromoheptyloxy)phenyl]bromobenzene

IR (KBr): 2935.1, 2856.1, 1604.5 cm^{-1}

NMR ($CDCl_3$, δ): 1.18–1.65 (6 H, m), 1.70–2.02 (4 H,m), 3.41 (2 H, t, J=6.8 Hz), 3.99 (2 H, t, J=6.4 Hz), 6.95 (2 H, d, J=8.6 Hz), 7.40 (2 H, d, J=8.6 Hz), 7.46 (2 H, d, J=8.6 Hz), 7.52 (2 H, d, J=8.6 Hz)

Preparation 86

4-[4-(8-Bromooctyloxy)phenyl]bromobenzene

NMR ($CDCl_3$, δ): 1.22–1.65 (8 H, m), 1.65–1.95 (4 H, m), 3.41 (2 H, t, J=6.8 Hz), 3.99 (2 H, t, J=6.4 Hz), 6.95 (2 H, d, J=8.6 Hz), 7.40 (2 H, d, J=8.6 Hz), 7.46 (2 H, d, J=8.6 Hz), 7.52 (2 H, d, J=8.6 Hz)

Preparation 87

Methyl (E)-3-[4-[4-(5-hexenyloxy)phenyl]phenyl] acrylate

NMR ($CDCl_3$, δ): 1.50–1.72 (2 H, m) 1.72–1.95 (2 H, m), 2.05–2.14 (2 H,m), 3.82 (3 H, s), 4.01 (2 H, t, J=6.3 Hz), 4.94–5.10 (2 H, m), 5.70–5.93 (1 H, m), 6.46 (1 H, d, J=16

Hz), 6.97 (2 H, d, J=8.7 Hz), 7.54 (2 H, d, J=8.7 Hz), 7.58 (4 H, s), 7.72 (1 H, d, J=16 Hz)

APCI-MASS: m/z=337 (M^++1)

Preparation 88

4-Bromo-4'-(4-methylpentyloxy)biphenyl

IR (KBr): 2956.3, 2871.5, 1606.4 cm^{-1}

NMR ($CDCl_3$, δ): 0.93 (6 H, d, J=6.6 Hz), 1.25–1.45 (2 H, m), 1.62 (1 H, sept, J=6.6 Hz), 1.72–1.93 (2 H, m), 3.98 (2 H, t, J=6.6 Hz), 6.95 (2 H, d, J=8.6 Hz), 7.30–7.60 (6 H, m)

APCI-MASS: m/z=332, 334 (M^+, M^++2)

The follwoing compounds (Preparations 89 to 90) were obtained according to a similar manner to that of Preparation 2.

Preparation 89

N-[4-[2-(4-Methylpentyl)-2,3-dihydro-4 H-1,2,4-triazol-3-one-4-yl]phenyl]piperazine ditrifluoroacetate

IR (KBr): 1668.1, 1519.6, 1203.4, 1176.4, 1130.1 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (6 H, d, J=6.6 Hz), 1.1–1.3 (2 H, M0, 1.4–1.8 (3 H, m), 3.1–3.3 (4 H, m), 3.3–3.5 (4 H, m), 3.70 (2 H, t, J=7.0 Hz), 7.11 (2 H, d, J=9.0 Hz), 7.53 (2 H, d, J=9.0 Hz), 8.35 (1 H, s), 8.90 (2 H, s)

Preparation 90

1-(4-Phenylcyclohexyl)piperazine ditrifluoroacetate

IR (KBr): 1677.8, 1197.6, 1133.9 cm^{-1}

NMR (DMSO-d_6, δ): 1.4–1.8 (4 H, m), 1.8–2.25 (4 H, m), 2.4–2.7 (1 H, m) 3.2–3.7 (9 H, m, 4.54 (2 H, br s)s, 7.0–7.4 (5 H, m), 9.32 (1 H, br s)

APCI-MASS:m/z=245 (M^++H)

The following compounds (Preparations 91 to 103) were obtained according to a similar manner to that of Preparation 3.

Preparation 91

Methyl 6-[4-(4-octyloxyphenyl)piperazin-1-yl] nicotinate

IR (KBr): 2923, 1726, 1608, 1515, 1278, 1116 cm^{-1}

NMR ($CDCl_3$, δ): 0.88 (3 H, t, J=6.8 Hz), 1.2–1.5 (10 H, m), 1.7–1.8 (2 H, m), 3.1–3.2 (4 H, m), 3.8–4.0 (9 H, m), 6.64 (1 H, d, J=9.0 Hz), 6.8–7.0 (4 H, m), 8.04 (1 H, dd, J=9.0 and 2.4 Hz), 8.81 (1 H, d, J=2.4 Hz)

APCI-MASS: m/z=426 (M+H^+)

Preparation 92

4-[4-[4-[2-(4-Methylpentyl)-2,3-dihydro-4 H-1,2,4-triazol-3-one-4-yl]phenyl]piperazin-1-yl]benzonitrile

IR (KBr): 2217.7, 1685.5 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (6 H, d, J=6.6 Hz), 1.2–1.4 (2 H, m), 1.5–2.0 (3 H, m), 3.3–3.4 (4 H, m), 3.4 –3.6 (4 H, m), 3.83 (2 H, t, J=7.4 Hz), 6.92 (2 H, d, J=9.0 Hz), 7.01 (2 H, d, J=9.0 Hz), 7.43 (2 H, d, J=9.0 Hz), 7.54 (2 H, d, J=9.0 Hz), 7.62 (1 H, s)

Preparation 93

3-Fluoro-4-[4-(4-methoxyphenyl)piperazin-1-yl] benzonitrile

IR (KBr): 2225.5, 1510.0, 1240.0 cm^{-1}

NMR ($CDCl_3$, δ): 3.1–3.55 (8 H, m), 3.79 (3 H, s), 6.7–7.1 (6 H, m), 7.3–7.5 (1 H, m)

Preparation 94

3-Chloro-4-[4-(4-n-hexyloxyphenyl)piperazin-1-yl] benzonitrile

IR (KBr): 2223.5, 1592.9, 1510.0, 1490.7, 1236.1 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3 H, t, J=6.7 Hz), 1.3–1.6 (6 H, m), 1.7–1.9 (2 H, m), 3.2–3.4 (8 H, m), 3.92 (2 H, t, J=6.6 Hz), 6.85 (2 H, d, J=9.3), 6.94 (2 H, d, J=9.3 Hz), 7.08 (1 H, d, J=8.4 Hz), 7.53 (1 H, dd, J=8.4 and 1.9 Hz), 7.64 (1 H, d, J=1.9 Hz)

APCI-MASS: m/z=398 (M^++H)

Preparation 95

Ethyl 3-[4-(4-n-hexyloxyphenyl)piperazin-1yl]-6-pyridazinecarboxylate

IR (KBr): 1729.8, 1587.1, 1511.9, 1245.8 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3 H, t, J=6.5 Hz), 1.2–1.4 (6 H, m), 1.44 (3 H, t, J=7.1 Hz), 1.65–1.85 (2 H, m), 3.1–3.25 (4 H, m), 3.8–4.0 (6 H, m), 4.46 (2 H, q, J=7.1 Hz), 6.8–7.0 (5 H, m), 7.91 (1 H, d, J=9.6 Hz)

APCI-MASS: m/z=413 (M^++H)

Preparation 96

4-(4-Piperidinopiperidin-1-yl)benzonitrile

IR (KBr): 2217.7, 1602.6, 1511.9 cm^{-1}

NMR ($CDCl_3$, δ): 1.35–1.75 (8 H, m), 1.92 (2 H, d, J=12.9 Hz), 2.3–2.6 (5 H, m), 2.86 (2 H, td, J=12.8 and 2.6 Hz), 3.90 (2 H, d, J=12.8 Hz), 6.84 (2 H, d, J=9.1 Hz), 7.46 (2 H, d, J=9.1 Hz)

APCI-MASS: m/z=270 (M^++H)

Preparation 97

5-[4-(4-n-Hexyloxyphenyl)piperazin-1-yl] picolinonitrile

Ir (KBr): 2223.5, 1575.6, 1511.9, 1241.9 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3 H, t, J=6.5 Hz), 1.2–1.55 (6 H, m), 1.7–1.85 (2 H, m), 3.22 (4 H, t, J=5.2 Hz), 3.52 (4 H, t, J=5.1 Hz), 3.92 (2 H, t, J=6.5 Hz), 6.86 (2 H, d, J=9.4 Hz), 6.93 (2 H, d, J=9.4 Hz), 7.13 (1 H, dd, J=8.8 and 3.0 Hz), 7.53 (1 H, d, J=8.8 Hz), 8.35 (1 H, d, J=3.0 Hz)

APCI-MASS: m/z=365 (M^++H)

Preparation 98

4-[4-(4-Cyclohexylphenyl)piperazin-1-yl] benzonitrile

IR (KBr): 2219.7, 1606.4, 1513.8, 1238.1 cm^{-1}

NMR ($CDCl_3$, δ): 1.1–1.5 (6 H, m), 1.65–2.0 (4 H, m), 2.44 (1 H, m), 3.30 (4 H, t, J=5.1 Hz), 3.46 (4 H, t, J=5.1 Hz), 6.90 (4 H, d, J=8.9 Hz), 7.14 (2 H, d, J=8.9 Hz), 7.52 (2 H, d, J=8.9 Hz)

APCI-MASS: m/z=346 (M^++H)

Preparation 99

4-[4-(4-n-Hexylphenyl)piperazin-1- yl]benzonitrile

IR (KBr): 2925.5, 2850.3, 2213.9, 1604.5, 1513.8, 1234.2, 944.9 cm^{-1}

NMR ($CDCl_3$, δ): 0.88 (3 H, t, J=6.4 Hz), 1.2–1.45 (6 H, m), 1.45–1.7 (2 H, m), 2.54 (2 H, t, J=7.6 Hz), 3.2–3.4 (4 H, m), 3.4–3.6 (4 H, m), 6.89 (2 H, d, J=8.5 Hz), 6.91 (2 H, d, J=8.9 Hz), 7.11 (2 H, d, J=8.5 Hz), 7.52 (2 H, d, J=8.9 Hz)

Preparation 100

1-[2-(4-n-Hexylphenylamino)ethyl]-2-oxazolidone hydrochloride

IR (KBr): 2925.5, 2852.2, 1753.0, 1729.8, 1267.0 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3 H, t, J=6.5 Hz), 1.1–1.4 (6 H, m), 1.45–1.7 (2 H, m), 2.56 (2 H, t, J=7.6 Hz), 3.3–3.53 (4 H, m), 3.57 (2 H, t, J=7.9 Hz), 4.24 (2 H, t, J=7.9 Hz), 7.24 (4 H, s)

APCI-MASS: m/z=291 (M^++H)

Preparation 101

4-[4-(4-Phenylcyclohexyl)piperazin-1-yl] benzonitrile

IR (KBr): 2212.0, 1602.6, 1513.8, 1249.6 cm^{-1}

NMR ($CDCl_3$, δ): 1.3–1.8 (4 H, m), 1.9–2.2 (4 H, m), 2.3–2.6 (2 H, m), 2.75 (4 H, t, J=5.0 Hz), 3.34 (4 H, t, J=5.0 Hz), 6.86 (2 H, d, J=8.9 Hz), 7.1–7.4 (5 H, m), 7.49 (2 H, d, J=8.9 Hz)

APCI-MASS: m/z=346 (M^++H)

Preparation 102

Methyl 6-[4-(4-hydroxyphenyl)piperazin-1-yl] nicotinate

IR (KBr): 3411, 1691, 1602, 1510, 1432, 1249, 1147 cm^{-1}

NMR (DMSO-d_6, δ): 3.0–3.1 (4 H, m), 3.7–3.9 (7 H, m), 6.67 (2 H, d, J=8.8 Hz), 6.84 (2 H, d, J=8.8 Hz), 6.93 (1 H, d, J=9.1 Hz), 7.97 (1 H, dd, J=2.4 and 9.1 Hz), 8.66 (1 H, d, J=2.4 Hz), 8.88 (1 H, s)

APCI-MASS: m/z=314 $(M+H)^+$

Preparation 103

1-n-Decylindole-5-carboxylic acid

IR (KBr): 2921, 2854, 1679, 1612, 1427, 1313, 1199 cm^{-1}

NMR (DMSO-d_6, δ): 0.84 (3 H, t, J=6.8 Hz), 1.1–1.3 (14 H, m), 1.6–1.8 (2 H, m), 4.19 (2 H, t, J=6.9 Hz), 6.57 (1 H, s), 7.4–7.8 (3 H, m), 8.23 (1 H, s), 12.40 (1 H, s)

APCI-MASS: m/z=302 $(M+H^+)$

The following compounds (Preparations 104 to 111) were obtained according to a similar manner to that of Preparation 10.

Preparation 104

(E)-Methyl 4-(4-n-butoxyphenyl)cinnamate

IR (KBr): 2958, 2939, 2873, 1720, 1637, 1498, 1313, 1195, 1170 cm^{-1}

NMR ($CDCl_3$, δ): 0.98 (3 H, t, J=7.3 Hz), 1.4–1.8 (4 H, m), 3.81 (3 H, s), 4.00 (2 H, t, J=6.4 Hz), 6.45 (1 H, d, J=16.0 Hz), 6.97 (2 H, d, J=8.7 Hz), 7.5–7.7 (6 H, m), 7.72 (1 H, d, J=16.0 Hz) APCI-MASS: m/z=311 $(M+H^+)$

Preparation 105

Methyl (E)-3-[4-[4-(4-methylpentyloxy)phenyl] phenyl]acrylate

IR (KRb): 2956.3, 2873.4, 1720.2, 1635.3, 1600.6 cm^{-1}

NMR ($CDCl_3$, δ): 0.93 (6 H, d, J=6.5 Hz), 1.28–1.50 (2 H, m), 1.50–1.95 (3 H, m), 3.82 (3 H, s), 3.99 (2 H, t, J=6.6 Hz), 6.44 (1 H, d, J=16.0 Hz), 6.97 (2 H, d, J=8.7 Hz), 7.49–7.65 (6 H, m), 7.71 (1 H, d, J=16 Hz)

APCI-MASS: m/z=339 (M^++1)

Preparation 106

Methyl (E)-3-[4-[4-(6-flurohexyloxy)phenyl]phenyl] acrylate

NMR ($CDCl_3$, δ): 1.23–2.00 (8 H, m), 3.81 (3 H, s), 4.01 (2 H, t, J=6.4 Hz), 4.47 (2 H, dt, J=47.4 and 6.0), 6.45 (1 H, d, J=16.0 Hz), 6.96 (2 H, d, J=8.8 Hz), 7.45–7.63 (6 H, m), 7.72 (1 H, d, J=16.0 Hz)

APCI-MASS: m/z=357 (M^++1)

Preparation 107

Methyl (E)-3-[4-[4-(6-methoxyhexyloxy)phenyl] phenyl]acrylate

APCI-MASS: m/z=369 (M^+)

Preparation 108

Methyl (E)-3-[4-[4-(8-methoxyoctyloxy)phenyl] phenyl]acrylate

IR (KBr): 2935.1, 2858.0, 1722.1, 1637.3, 1602.6 cm^{-1}

NMR ($CDCl_3$, δ): 1.3–1.70 (10 H, m), 1.70–1.92 (2 H, m), 3.33 (3 H, s), 3.37 (2 H, t, J=6.5 Hz), 3.81 (3 H, s), 4.00 (2 H, t, J=6.5 Hz), 6.45 (1 H, d, J=16.0 Hz), 6.97 (2 H, d, J=8.8 Hz), 7.46–7.78 (6 H, m), 7.72 (1 H, d, J=16.0 Hz)

APCI-MASS: m/z=397 (M^++1)

Preparation 109

Methyl (E)-3-[4-(4-hydroxyphenyl)phenyl]acrylate

IR (KBr): 3409.5, 1695.1 cm^{-1}

NMR (DMSO-d_6, δ): 3.73 (3 H, s), 6.64 (1 h, d, J=16 Hz), 6.85 (2 H, d, J=8.6 Hz), 7.50–7.83 (5 H, m)

APCI-MASS ;: m/z=255 (M^++1)

Preparation 110

Methyl (E)-3-[4-[4-(7-methoxyheptyloxy)phenyl] phenyl]acrylate

NMR ($CDCl_3$, δ): 1.32–1.70 (8 H, m), 1.70–1.92 (2 H, m), 3.34 (3 H, s), 3.38 (2 H, t, J=6.4 Hz), 3.81 (3 H, s), 4.00 (2 H, t, J=6.5 Hz), 6.45 (1 H, d, J=16.0 Hz), 6.97 (2 H, d, J=8.8 Hz), 7.47–7.65 (6 H, m), 7.70 (1 H, d, J=16 Hz)

APCI-MASS: m/z=383 (M^++1)

Preparation 111

Methyl (E)-3-[4-[4-(7-fluoroheptyloxy)phenyl] phenyl]acrylate

IR (KBr): 2937.1, 2861.8, 1722.1, 1637.3, 1600.6 cm^{-1}

The following compound was obtained according to a similar manner to that of Preparation 20.

Preparation 112

Methyl 3-[4-(4-heptylphenyl)phenyl]propanoate

NMR ($CDCl_3$, δ): 0.88 (3 H, t, J=6.5 Hz), 1.15–1.50 (8 H, m), 1.5–1.77 (2 H, m), 2.52–2.73 (4 H, m), 2.99 (2 H, t, J=7.8 Hz), 3.68 (3 H, s), 7.18–7.35 (4 H, m), 7.40–7.58 (4 H, m)

APCI-MASS: m/z=339)M^++1)

The followng compounds (Preparation 113 to 164) were obtained according to a similar manner to that of Preparation 32.

Preparation 113

4-(4-Octylphenyl)-2,4-dihydro-3 H-1,2,4-triazol-3-one-2-yl-acetic acid

IR (KBr): 2923.6, 1704.8, 1224.6 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3 H, t, J=6.7 Hz), 1.1–1.4 (10 H, m), 1.4–1.7 (2 H,m), 2.60 (2 H, t, J=7.2 Hz), 4.38 (2 H, s), 7.32 (2 H, d, J=8.5 Hz), 7.58 (2 H, d, J=8.5 Hz), 8.43 (1 H, s)

Preparation 114

1-Heptyl-4-(4-carboxyphenyl)pyrazole

IR (KBr): 3106, 2917, 1687, 1612, 1425, 1295, 1184, 952, 860, 773 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3 H, t, J=6.8 Hz), 1.1–1.4 (8 H, m), 1.7–1.9 (2 H, m), 4.11 (2 H, t, J=7.0 Hz), 7.69 (2 H, d, J=8.5 Hz), 7.91 (2 H, d, J=8.5 Hz), 7.98 (1 H, s), 8.32 (1 H, s), 12.82 (1 H, br)

APCI-MASS: m/z=287 ($M+H^+$)

Preparation 115

6-[4-(4-Octyloxyphenyl)piperazin-1-yl]nicotinic acid

IR (KBr pelet): 2919, 2854, 1697, 1608, 1515, 1429, 1263, 1245, 1228 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 1.1–1.5 (10H, m), 1.6–1.8 (2H, m), 3.0–3.2 (4H, m), 3.7–3.9 (4H, m), 3.88 (2H, t, J=6.4 Hz), 6.7–7.0 (5H, m), 7.95 (1H, dd, J=9.0 and 1.1 Hz), 8.64 (1H, d, J=1.1 Hz)

APCI-MASS: m/z=412 ($M+H^+$)

Preparation 116

2-(4-Hexyloxyphenyl)benzoxazole-5-carboxylix acid

IR (KBr): 2952, 1689, 1677, 1619, 1500, 1415, 1299, 1172, 1024 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (3H, t, J=6.7 Hz), 1.2–1.5 (6H, m), 1.7–1.9 (2H, m), 4.09 (2H, t, J=6.5 Hz), 7.16 (2H, d, J=8.8 Hz), 7.84 (1H, d, J=8.5 Hz), 8.01 (1H, dd, J=8.5 and 1.5 Hz), 8.15 (2H, d, J=8.8 Hz), 8.26 (1H, d, J=1.5 Hz)

APCI-MASS: m/z=340 ($M+H^+$)

Preparation 117

4-[4-(4-n-Butyloxyphenyl)phenyl]benzoic acid

IR (KBr): 2958, 2873, 1689, 1600, 1537, 1396 cm^{-1}

Preparation 118

6-(4-Heptyloxyphenyl)nicotinic acid

IR (KBr): 2858, 1699, 1674, 1589, 1425, 1180, 1016, 781 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.7 Hz), 1.2–1.5 (8H, m), 1.6–1.8 (2H, m), 4.04 (2H, t, J=6.4 Hz), 7.06 (2H, d, J=8.9 Hz), 8.03 (1H, d, J=8.2 Hz), 8.13 (2H, d, J=8.9 Hz), 8.27 (1H, dd, J=8.2 and 2.2 Hz), 9.09 (1H, d, J=2.2 Hz), 13.31 (1H, br)

APCI-MASS: m/z=314 ($M+H^+$)

Preparation 119

5-(4-Octyloxyphenyl)isoxazole-3-carboxylic acid

IR (KBr pelet): 2923, 2852, 1704, 1612, 1440, 1272, 1178 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.8 Hz), 1.2–1.6 (10H, m), 1.6–1.9 (2H, m), 4.03 (2H, t, J=6.5 Hz), 7.08 (2H, d, J=8.9 Hz), 7.25 (1H, s), 7.86 (2H, d, J=8.9 Hz)

APCI-MASS: m/z=318 ($M+H^+$)

Preparation 120

2-(2-Octyloxypyridin-5-yl)benzoxazole-5-carboxylic acid

IR (KBr): 2954, 2923, 2854, 1697, 1683, 1625, 1488, 1290 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=7.6 Hz), 1.2–1.5 (10H, m), 1.7–1.8 (2H, m), 4.36 (2H, t, J=6.6 Hz), 7.04 (1H, d, J=8.7 Hz), 7.88 (1H, d, J=8.5 Hz), 8.04 (1H, dd, J=8.5 and 1.6 Hz), 8.29 (1H, d, J=1.6 Hz), 8.43 (1H, dd, J=8.7 and 2.4 Hz), 8.99 (1H, d, J=2.4 Hz), 13.0–13.2 (1H, br)

APCI-MASS: m/z=369 ($M+H^+$)

Preparation 121

2-[4-(4-Hexylphenyl)phenyl]benzoxazole-5-carboxylic acid

Ir (KBr): 2923, 2854, 1683, 1411, 1299, 1054 cm^{-1}

APCI-MASS: m/z=400 ($M+H^+$)

Preparation 122

6-[4-(4-n-Butyloxyphenyl)phenyl]nicotinic acid

IR (KBr): 3406, 2958, 1691, 1591, 1394, 1284, 1253 cm^{-1}

NMR (DMSO-d_6, δ): 0.94 (3H, t, J=7.3 Hz), 1.4–1.8 (4H, m), 4.01 (2H, t, J=6.4 Hz), 7.02 (2H, d, J=8.7 Hz), 7.57 (2H, d, J=8.7 Hz), 7.61 (2H, d, J=8.2 Hz), 7.83 (2H, d, J=8.2 Hz), 8.05 (1H, d, J=8.5 Hz), 8.22 (1H, dd, J=8.5 and 1.6 Hz), 9.14 (1H, d, J=1.6 Hz)

APCI-MASS: m/z=348 ($M+H^+$)

Preparation 123

4-[4-(5-Phenoxypentyloxy)phenyl]benzoic acid

NMR (DMSO-d_6, δ): 1.5–1.7 (2H, m), 1.7–1.9 (4H, m), 3.98 (2H, t, J=6.3 Hz), 4.05 (2H, t, J=6.1 Hz), 6.8–7.0 (3H, m), 7.05 (2H, d, J=8.6 Hz), 7.25 (2H, t, J=8.2 Hz), 7.68 (2H, d, J=8.5 Hz), 7.75 (2H, d, J=8.2 Hz), 7.98 (2H, d, J=8.2 Hz), 12.8–13.0 (1H, br s)

APCI-MASS: m/z=375 $(M-H)^-$

Preparation 124

4-[5-(4-n-Hexyloxyphenyl)-1,3,4-oxadiazol-2-yl]benzoic acid

IR (KBr): 2935, 2854, 1685, 1612, 1495, 1425, 1286, 1251 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (3H, t, J=6.7 Hz), 1.2–1.5 (6H, m), 1.6–1.9 (3H, m), 4.12 (2H, t, J=6.4 Hz), 7.19 (2H, d,

J=8.7 Hz), 8.08 (2H, d, J=8.7 Hz), 8.18 (2H, d, J=8.4 Hz), 8.24 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=367 $(M+H)^+$

Preparation 125

4-[5-(4-n-Hexyloxyphenyl)-1,3,4-thiadiazol-2-yl] benzoic acid

IR (KBr): 2952, 2586, 1699, 1604, 1517, 1432, 1251, 1174 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (3H, t, J=6.7 Hz), 1.3–1.9 (8H, m), 4.04 (2H, t, J=6.3 Hz), 7.13 (2H, d, J=8.8 Hz), 7.97 (2H, d, J=8.8 Hz), 8.11 (4H, s)

APCI-MASS: m/z=383 $(M+H)^+$

Preparation 126

5-(4-Octyloxyphenyl)-1-methylpyrazole-3-carboxylic acid

IR (KBr pelet): 2950, 2923, 1695, 1450, 1282, 1251, 956 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.8 Hz), 1.2–1.5 (10H, m), 1.6–1.8 (2H, m), 3.98 (2H, t, J=6.5 Hz), 4.10 (3H, s), 6.95 (1H, d, J=8.8 Hz), 7.18 (1H, s), 7.73 (2H, d, J=8.8 Hz), 13.37 (1H, br)

APCI-MASS: m/z=331 $(M+H^+)$

Preparation 127

4-[3-(4-n-Pentyloxyphenyl)pyrazol-5-yl]benzoic acid

IR (KBr): 3224, 2956, 1692, 1614, 1506, 1251 cm^{-1}

NMR (DMSO-d_6, δ): 0.91 (3H, t, J=6.9 Hz), 1.3–1.5 (4H, m), 1.6–1.8 (2H, m), 4.00 (2H, t, J=6.5 Hz), 7.02 (2H, d, J=8.8 Hz), 7.19 (1H, s), 7.75 (2H, d, J=8.8 Hz), 7.95 (2H, d, J=8.7 Hz), 8.02 (2H, d, J=8.7 Hz), 12.8–13.3 (2H, br)

APCI-MASS: m/z=351 $(M+H^+)$

Preparation 128

5-[4-(n-Butoxyphenyl)phenyl]furan-2-carboxylic acid

IR (KBr): 2958, 2873, 1679, 1487, 1253, 1166 cm^{-1}

NMR (DMSO-d_6, δ): 0.95 (3H, t, J=7.3 Hz), 1.3–1.8 (4H, m), 4.02 (2H, t, J=6.3 Hz), 7.03 (2H, d, J=8.6 Hz), 7.17 (1H, d, J=3.6 Hz), 7.33 (1H, d, J=3.6 Hz), 7.66 (2H, d, J=8.6 Hz), 7.74 (2H, d, J=8.4 Hz), 7.86 (2H, d, J=8.4 Hz), 13.1 (1H, br s)

APCI-MASS: m/z=337 $(M+H)^+$

Preparation 129

3-(S)-Hydroxyhexadecanoic acid

IR (KBr): 1679.7, 1467.6, 1224.6 cm^{-1}

NMR ($CDCl_3$, δ): 0.88 (3H, t, =6.4 Hz), 1.1–1.7 (24H, m), 2.35–2.65 (2H, m), 4.03 (1H, m), 5.41 (1H, br

Preparation 130

6-[4-(4-n-Hexyloxyphenyl)piperazin-1-yl] pyridazine-3-carboxylic acid

IR (KBr): 1697.1, 1589.1, 1515.8, 1448.3 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.4 Hz), 1.2–1.5 (6H, m), 1.6–1.8 (2H, m), 3.0–3.2 (4H, m), 3.7–4.0 (6H, m), 6.83 (2H, d, J=9.0 Hz), 6.95 (2H, d, J=9.0 Hz), 7.36 (1H, d, J=9.6 Hz), 7.86 (1H, d, J=9.6 Hz), 11.68 (1H, s)

Preparation 131

4-[4-[1-(4-n-Hexyloxyphenyl)piperidin-4-yl] piperazin-1-yl]benzoic acid hydrochloride

IR (KBr): 1699.0, 1608.3, 1513.8 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.5 Hz), 1.2–1.5 (6H, m), 1.6–1.8 (2H, m), 2.0–2.45 (3H, m), 3.2–3.8 (12H, m), 3.94 (2H, t, J=6.4 Hz), 4.03 (2H, d, J=11 Hz), 6.95 (2H, d, J=8.7 Hz), 7.07 (2H, d, J=8.9 Hz) , 7.32 (2H, br s), 7.83 (2H, d, J=8.9 Hz)

APCI-MASS: m/z=466 $(M^+ + H)$

Preparation 132

6-(8-Methoxyoctyloxy)-2-naphthoic acid

IR (KBr): 2937.1, 2854.1, 1677.8, 1211.1 cm^{-1}

NMR (DMSO-d_6, δ): 1.2–1.6 (10H, m), 1.7–1.9 (2H, m), 3.20 (3H, s), 3.29 (2H, t, J=6.5 Hz), 4.11 (2H, t, J=6.4 Hz), 7.23 (1H, dd, J=9.0 and 2.3 Hz), 7.39 (1H, d, J=2.3 Hz), 7.85 (1H, d, J=8.7 Hz), 7.93 (1H, d, J=8.7 Hz), 7.99 (1H, d, J=9.0 Hz), 8.51 (1H, s), 12.9 (1H, s)

Preparation 133

Mixture of (E) and (Z)-3-[4-(4-Heptylphenyl) phenyl]-2-butenoic acid

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.6 Hz), 1.15–1.50 (8H, m), 1.52–1.75 (2H, m), 2.63 and 3.62 (total 3H, each s), 2.53–2.75 (2H, m), 6.24 and 5.68 (total 1H, each s), 7.19–7.35 (2H, m), 7.47–7.70 (6H, m)

APCI-MASS: m/z=337 $(M^+ + 1)$, 351 (methyl $ester^+ + 1$)

Preparation 134

3-[4-(4-Heptylphenyl)phenyl]propanoic acid

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.6 Hz), 1.13–1.48 (8H, m), 1.48–1.75 (2H, m), 2.52–2.83 (4H, m), 3.00 (2H, t, J=7.8 Hz), 7.15–7.35 (4H, m), 7.40–7.60 (4H, m)

APCI-MASS: m/z=323 $(M^+ - 1)$

Preparation 135

4-(4-n-Heptylphenyl)benzoyl-carboxylic acid

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.6 Hz), 1.13–1.50 (8H, m), 1.50–1.75 (2H, m), 2.66 (2H, t, J=7.7 Hz), 7.20–7.40 (2H, m), 7.50–7.66 (2H, m), 7.66–7.84 (2H, m), 8.40–8.60 (2H, m)

APCI-MASS: m/z=323 $(M^+ - 1)$

Preparation 136

6-Hexylnaphthalene-2-carboxylic acid

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.8 Hz), 1.15–1.53 (6H, m), 1.55–1.84 (2H, m), 2.80 (2H, t, J=7.6 Hz), 7.42 (1H, dd, J=1.7 and 8.4 Hz), 7.67 (1H, s), 7.84 (1H, d, J=8.6 Hz), 7.90 (1H, d, J=8.4 Hz), 8.09 (1H, dd, J=1.7 and 8.6 Hz), 8.68 (1H, s)

APCI-MASS: m/z=257 $(M^+ + 1)$, 271 (methyl $ester^+ + 1$)

Preparation 137

3-(E)-[4-[4-(7-Methoxyheptyloxy)phenyl]phenyl] acrylic acid

NMR (DMSO-d_6, δ): 1.20–1.60 (8H, m), 1.60–1.83 (2H, m), 3.21 (3H, s), 3.25–3.60 (2H, m), 4.01 (2H, t, J=6.4 Hz),

6.54 (1H, d, J=16.0 Hz), 7.02 (2H, d, J=8.8 Hz), 7.55–7.80 (7H, m)

APCI-MASS: m/z=369 (M^++1)

Preparation 138

3-(E)-[4-[4-(8-Methoxyoctyloxy)phenyl]phenyl] acrylic acid

IR (KBr): 3037.3, 2933.2, 2858.0, 2551.4, 1706.7, 1677.8, 1629.6, 1602.6 cm^{-1}

NMR (DMSO-d_6, δ): 1.18–1.55 (10H, m), 1.65–1.83 (2H, m), 3.18–3.45 (5H, m), 4.01 (2H, t, J=6.5 Hz), 6.53 (1H, d, J=16.0 Hz), 7.02 (2H, d, J=8.8 Hz), 7.50–8.80 (7H, m)

APCI-MASS: m/z=383 (M^++1)

Preparation 139

3-(E)-[4-[4-(5-Hexenyloxy)phenyl]phenyl]acrylic acid

NMR (DMSO-d_6, δ): 1.42 1.63 (2H, m), 1.63–1.85 (2H, m), 2.00–2.20 (2H, m), 4.03 (2H, t, J=6.3 Hz), 4.90–5.15 (2H, m), 5.68–5.97 (1H, m), 6.54 (1H, d, J=16 Hz), 7.02 (2H, d, J=8.7 Hz), 7.50–7.80 (7H, m)

APCI-MASS: m/z=323 (M^++1)

Preparation 140

3-(E)-[4-[4-(4-Methylpentyloxy)phenyl]phenyl] acrylic acid

IR (KBr): 2956.3, 2869.6, 2713.4, 2599.6, 1689.3, 1627.6, 1602.6 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (6H, d, J=6.5 Hz), 1.15–1.43 (2H, m), 1.48–1.90 (3H, m), 4.00 (2H, t, J=6.7 Hz), 6.54 (1H, d, J=16 Hz), 7.02 (2H, d, J=8.7 Hz), 7.50–7.90 (7H, m)

APCI-MASS: m/z=325 (M^++1)

Preparation 141

3-(E)-[4-[4-(6-Fluorohexyloxy)phenyl]phenyl] acrylic acid

NMR ($CDCl_3$, δ): 1.39–2.00 (8H, m), 4.01 (2H, t, J=6.5 Hz), 4.47 (2H, dt, J=47.3 and 6.0 Hz), 6.49 (1H, d, J=15.9 Hz), 6.98 (2H, d, J=8.7 Hz), 7.40–7.70 (6H, m), 7.81 (1H, d, J=15.9 Hz)

APCI-MASS: m/z=343 (M^++1)

Preparation 142

3-(E)-[4-[4-(6-Methoxyhexyloxy)phenyl]phenyl] acrylic acid

NMR (DMSO-d_6, δ): 1.22–1.63 (6H, m), 1.63–1.88 (2H, m), 3.21 (3H, s), 3.22–3.40 (2H, m), 4.00 (2H, t, J=6.5 Hz), 6.54 (1H, d, J=15.8 Hz), 7.02 (2H, d, J=8.7 Hz), 7.50–7.84 (7H, m)

APCI-MASS: m/z=369 (methyl ester, M^++1)

Preparation 143

4-[4-[8-(Tetrahydropyran-2-yloxy)octyloxy]phenyl] benzoic acid

IR (KBr): 2935, 1697, 1683, 1604, 1303, 1290, 1197 cm^{-1}

NMR (DMSO-d_6, δ): 1.2–1.8 (18H, m), 3.3–3.9 (4H, m), 4.01 (2H, t, J=6.3 Hz), 4.5–4.6 (1H, m), 7.03 (2H, d, J=8.7 Hz), 7.67 (2H, d, J=8.7 Hz), 7.74 (2H, d, J=8.3 Hz), 7.98 (2H, d, J=8.3 Hz)

APCI-MASS: m/z=425 ($M-H^+$)

Preparation 144

4-[3-(4-n-Hexyloxyphenyl)pyrazol-5-yl]benzoic acid

IR (KBr): 2956, 2935, 1693, 1614, 1508, 1432, 1251, 1178 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (3H, t, J=6.4 Hz), 1.2–1.5 (6H, m), 1.6–1.8 (2H, m), 4.00 (2H, t, J=6.4 Hz), 7.02 (2H, d, J=8.7 Hz), 7.12 (1H, s), 7.74 (2H, d, J=8.7 Hz), 7.95 (2H, d, J=8.8 Hz), 8.01 (2H, d, J=8.8 Hz), 13.17 (1H, s)

APCI-MASS: m/z=365 ($M+H^+$)

Preparation 145

4-[4-[4-(6-Methoxyhexyloxy)phenyl]phenyl]benzoic acid

IR (KBr): 2939, 2861, 1685, 1602, 1430, 1286, 1128 cm^{-1}

NMR (DMSO-d_6, δ): 1.3–1.8 (8H, m), 3.21 (3H, s), 3.3–3.4 (2H, m), 4.01 (2H, t, J=6.5 Hz), 7.04 (2H, d, J=8.6 Hz), 7.66 (2H, d, J=8.6 Hz), 7.7–7.9 (6H, m), 8.03 (2H, d, J=8.2 Hz)

APCI-MASS: m/z=405 ($M+H^+$)

Preparation 146

4-[5-[4-(8-Methoxyoctyloxy)phenyl]-1,3,4-thiadiazol-2-yl]benzoic acid

IR (KBr): 2931, 2854, 1691, 1602, 1251 cm^{-1}

NMR (DMSO-d_6, δ): 1.2–2.0 (12H, m), 3.20 (3H, s), 3.29 (2H, t, J=6.4 Hz), 4.04 (2H, t, J=4.6 Hz), 7.13 (2H, t, J=8.8 Hz), 7.9–8.2 (6H, m), 13.95 (1H, br)

APCI-MASS: m/z=441 ($M+H^+$)

Preparation 147

4-(4-n-Butoxyphenyl)cinnamic acid

IR (KBr): 2958, 2871, 1695, 1625, 1498, 1249 cm^{-1}

NMR (DMSO-d_6, δ): 0.94 (3H, t, J=7.3 Hz), 1.44 (2H, tq, J=7.0 and 7.3 Hz), 1.71 (2H, tt, J=7.0 and 6.4 Hz), 4.01 (2H, t, J=6.4 Hz), 6.54 (1H, d, J=16.0 Hz), 7.02 (2H, d, J=8.7 Hz), 7.6–7.9 (7H, m)

APCI-MASS: m/z=297 ($M+H^+$)

Preparation 148

4-[4-(4-Cyclohexylphenyl)-1,3,4-thiadiazol-2-yl] benzoic acid

IR (KBr): 2925, 2850, 1683, 1429, 1292 cm^{-1}

NMR (DMSO-d_6, δ): 1.1–1.5 (5H, m), 1.6–2.0 (5H, m), 2.4–2.6 (1H, m), 7.45 (2H, d, J=8.3 Hz), 7.96 (2H, d, J=8.3 Hz), 8.13 (4H, s)

APCI-MASS: m/z=365 $(M+H)^+$

Preparation 149

4-[5-[4-(Piperidin-1-yl)phenyl]-1,3,4,-thiadiazol-2-yl]benzoic acid

IR (KBr): 2931, 2854, 1685, 1604, 1415, 1238 cm^{-1}

NMR (DMSO-d_6, δ): 1.61 (6H, s), 3.31 (4H, s), 7.05 (2H, d, J=9.0 Hz), 7.83 (2H, d, J=9.0 Hz), 8.10 (4H, s)

APCI-MASS: m/z=366 $(M+H)^+$

Preparation 150

4-[5-[4-[4-n-Propyloxyphenyl)phenyl]-1,3,4-oxadiazol-2-yl]benzoic acid

IR (KBr): 2939, 1689, 1606, 1488, 1429, 1290 cm^{-1}

NMR (DMSO-d_6, δ): 1.00 (3H, t, J=7.3 Hz), 1.76 (2H, tq, J=6.5 and 7.3 Hz), 4.00 (2H, t, J=6.5 Hz), 7.07 (2H, d, J=8.8 Hz), 7.70 (2H, d, J=8.5 Hz), 7.78 (2H, d, J=8.8 Hz), 7.90 (2H, d, J=8.5 Hz), 8.0–8.4 (4H, m)

APCI-MASS: m/z=401 $(M+H)^+$

Preparation 151

4-(5-n-Nonyl-1,3,4-oxadiazol-2-yl)benzoic acid

IR (KBr): 2919, 2852, 1685, 1565, 1430, 1284 cm^{-1}

NMR (DMSO-d_6, δ): 0.84 (3H, t, J=6.5 Hz), 1.2–1.5 (12H, m), 1.7–1.9 (2H, m), 2.94 (2H, t, J=7.4 Hz), 8.0–8.2 (4H, m), 13.35 (1H, s)

APCI-MASS: m/z=317 $(M+H^+)$

Preparation 152

4-[3-(4-n-Hexyloxyphenyl)-1,2,4-oxadiazol-5-yl] benzoic acid

IR (KBr): 2942, 2869, 1695, 1421, 1251 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (3H, t, J=6.8 Hz), 1.2–1.8 (8H, m), 4.06 (2H, t, J=6.5 Hz), 7.13 (2H, d, J=8.9 Hz), 8.03 (2H, d, J=8.9 Hz), 8.17 (2H, d, J=8.5 Hz), 8.28 (2H, d, J=8.5 Hz)

APCI-MASS: m/z=367 $(M+H)^+$

Preparation 153

4-[4-[4-(5-Methoxypentyloxy)phenyl]phenyl] phenylacetic acid

IR (KBr): 2939, 2861, 1699, 1253, 1182, 1124 cm^{-1}

NMR (DMSO-d_6, δ): 1.4–1.9 (6H, m), 3.22 (3H, s), 3.39 (2H, t, J=6.12 Hz), 3.61 (2H, s), 4.01 (2H, t, J=6.4 Hz), 7.02 (2H, d, J=8.8 Hz), 7.35 (2H, d, J=8.2 Hz), 7.6–7.8 (8H, m)

APCI-MASS: m/z=405 $(M+H^{30})$

Preparation 154

4-[5-(4n-Octyloxyphenyl)-1,3,4-thiadiazol-2-yl] benzoic acid

IR (KBr): 2921, 2856, 1691, 1432, 1251 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.7 Hz), 1.2–1.5 (10H, m), 1.7–1.9 (2H, m), 4.07 (2H, t, J=6.5 Hz), 7.13 (2H, d, J=8.9 Hz), 7.97 (2H, d, J=8.9 Hz), 8.12 (4H, s)

APCI-MASS: m/z=411 $(M+H^+)$

Preparation 155

4-[5-(4-Trans-n-pentylcyclohexyl)-1,3,4-thiadiazol-2-yl]benzoic acid

IR (KBr): 2919, 2848, 1677, 1430, 1294 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.9 Hz), 1.0–1.4 (11H, m), 1.5–1.6 (2H, m), 1.8–2.0 (2H, m), 2.1–2.3 (2H, m), 3.1–3.3 (1H, m), 8.07 (4H, s)

APCI-MASS: m/z=359 $(M+H^+)$

Preparation 156

4-[3(4-n-Pentyloxyphenyl)isoxazol-5-yl]benzoic acid

IR (KBr): 2925, 2869, 1699, 1687, 1612, 1432, 1251, 1178 cm^{-1}

NMR (DMSO-d_6, δ): 0.91 (3H, t, J=6.9 Hz), 1.2–1.5 (4H, m), 1.7–1.9 (2H, m), 4.04 (2H, t, J=6.5 Hz), 7.09 (2H, d, J=8.8 Hz), 7.69 (1H, s) 7.85 (2H, d, J=8.8 Hz), 8.01 (2H, d, J=8.5 Hz), 8.11 (2H, d, J=8.5 Hz)

APCI-MASS: m/z=352 $(M+H^+)$

Preparation 157

4-[5-[4-(8-Methoxyoctyloxy)phenyl]-1,3,4-oxadiazol-2-yl]benzoic acid

IR (KBr): 2967, 2937, 2877, 1687, 1290 cm^{-1}

NMR (DMSO-d_6, δ): 1.2–1.6 (10H, m), 1.7–1.9 (2H, m), 3.20 (3H, s), 3.29 (2H, t, J=6.4 Hz), 4.08 (2H, t, J=6.5 Hz), 7.17 (2H, d, J=8.9 Hz), 8.07 (2H, d, J=8.9 Hz), 8.15 (2H, d, J=8.6 Hz), 8.24 (2H, d J=8.6 Hz)

APCI-MASS: m/z=425 $(M+H)^+$

Preparation 158

4-[4-(6-Phenylpyridazin-3-yl-oxy)phenyl]benzoic acid

IR (KBr): 1700, 1687, 1608, 1427, 1284, 1186 cm^{-1}

NMR (DMSO-d_6, δ): 7.4 (2H, d, J=8.6 Hz), 7.5–7.7 (4H, m) 7.7–7.9 (4H, m) 7.9–8.1 (4H, m), 8.35 (1H, d, J=9.2 Hz), 12.99 (1H, br s)

APCI-MASS: m/z=369 $(M+H)^+$

Preparation 159

4-[5-(4n-Octyloxyphenyl)-1,3,4-oxadiazol-2-yl] benzoic acid

IR (KBr): 2921, 2852, 1685, 1612, 1496, 1425, 1288, 1251 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.7 Hz), 1.2–1.5 (10H, m), 1.7–1.9 (2H, m), 4.08 (2H, t, J=6.4 Hz), 7.17 (2H, d, J=8.7 Hz), 8.07 (2H, d, J=8.7 Hz), 8.15 (2H, d, J=8.5 Hz), 8.24 (2H, d, J=8.5 Hz), 13.36 (1H, br)

APCI-MASS: m/z=395 $(M+H^+)$

Preparation 160

4-[2-(4-n-Hexyloxyphenyl)pyrimidin-6-yl]benzoic acid

IR (KBr): 2944, 2863, 1697, 1585, 1415, 1386, 1253 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (3H, t, J=6.7 Hz), 1.2–1.6 (6H, m), 1.7–1.9 (2H, m), 4.07 (2H, t, J=6.6 Hz), 7.10 (2H, d, J=8.9 Hz), 8.00 (1H, d, J=5.2 Hz, 8.13 (2H, d, J=8.4 Hz), 8.44 (2H, d, J=5.9 Hz), 8.47 (2H, d, J=5.9 Hz), 8.95 (1H, d, J=5.2 Hz)

APCI-MASS: m/z=377 $(M+H^+)$

Preparation 161

4-[4-(7-Piperidinocarbonylheptyloxy)phenyl]benzoic acid

IR (KBr): 2933, 2858, 1697, 1677, 1637, 1604, 1429, 1249 cm^{-1}

NMR (DMSO-d_6, δ): 1.2–1.8 (16H, m), 2.26 (2H, t, J=7.5 Hz), 3.2–3.5 (4H, m), 4.01 (2H, t, J=6.4 Hz), 7.03 (2H, d, J=8.8 Hz), 7.67 (2H, d, J=8.8 Hz), 7.74 (2H, d, J=8.4 Hz), 7.98 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=424 ($M+H^+$)

Preparation 162

6-[4-(4n-Heptyloxyphenyl)piperazin-1-yl]nicotinic acid

IR (KBr): 2929, 2854, 1695, 1673, 1606, 1577, 1515, 1421, 1245 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 1.2–1.5 (8H, m), 1.6–1.8 (2H, m), 3.0–3.2 (4H, m), 3.6–3.8 (4H, m), 3.87 (2H, t, J=6.5 Hz), 6.8–7.2 (5H, m), 7.95 (1H, dd, J=8.9 and 2.3 Hz), 8.62 (1H, d, J=2.3 Hz)

APCI-MASS: m/z=398 ($M+H^+$)

Preparation 163

6-[4-[4-(8-Methoxyoctyloxy)phenyl]piperazin-1-yl] nicotinic acid

IR (KBr): 2933, 2856, 1697, 1672, 1605, 1511, 1421, 1245 cm^{-1}

NMR (DMSO-d_6, δ): 1.2–1.8 (12H, m), 3.08 (4H, t, J=5.0 Hz), 3.20 (3H, s), 3.28 (2H, t, J=6.5 Hz), 3.78 (4H, t, J=4.6 Hz), 3.87 (2H, t, J=6.4 Hz), 6.8–7.0 (5H, m), 7.95 (1H, dd, J=9.0 and 2.2 Hz), 8.65 (1H, d, J=2.2 Hz), 12.54 (1H, s)

APCI-MASS: m/z=442 ($M+H^+$)

Preparation 164

4-[5-[4-(4-n-Propyloxyphenyl)phenyl]-1,3,4-thiadiazol-2-yl]benzoic acid

IR (KBr): 1685, 1537, 1423, 817 cm^{-1}

NMR (DMSO-d_6, δ): 1.00 (3H, t, J=6.7 Hz), 1.6–1.8 (2H, m), 4.00 (2H, t, J=6.6 Hz), 7.0–7.2 (2H, d, J=8.6 Hz), 7.6–8.1 (10H, m)

APCI-MASS: m/z=417 $(M+H)^+$

Preparation 165

To a solution of Ethyl 4-[5-(4-n-pentyloxyphenyl)-isoxazol-3-yl]benzoate (6.33 g) in ethanol 60 ml) and tetrahydrofuran (90 ml) was added 2N sodium hydroxide aqueous solution (12.5 ml) at 80° C. The mixture was refluxed for 1 hour and poured into ice-water. The suspension was adjusted to pH 2.0 with 1N HCl. The precipitate was collected by filtration, washed with water and dried to give 4-[5-(4-n-pentyloxyphenyl)isoxazol-3-yl]benzoic acid (5.80 g).

IR (KBr): 2939, 2867, 1681, 1614, 1429, 1255, 1178, 821 cm^{-1}

NMR (DMSO-d_6, δ): 0.91 (3H, t, J=7.1 Hz), 1.3–1.5 (4H, m), 1.6–1.8 (2H, m), 4.04 (2H, t, J=6.5 Hz), 7.11 (2H, d, J=8.9 Hz), 7.54 (1H, s), 7.85 (2H, d, J=8.9 Hz), 7.98 (2H, d, J=8.6 Hz), 8.11 (2H, d, J=8.6 Hz)

APCI-MASS: m/z=352 $(M+H)^+$

The following compounds (Preparations 166 to 170) were obtained according to a similar manner to that of Preparation 40.

Preparation 166

5-[4-(4-n-Hexyloxyphenyl)piperazin-1-yl]picolic acid trihydrochloride

IR (KBr): 1689.3, 1577.5, 1511.9, 1241.9 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.5 Hz), 1.15–1.5 (6H, m), 1.6–1.8 (2H, m), 3.1–3.25 (4H, m), 3.45–3.6 (4H, m), 3.89 (2H, t, J=6.4 Hz), 6.84 (2H, d, J=9.1 Hz), 6.97 (2H, d, J=9.1 Hz), 7.43 (1H, dd, J=8.8 and 3.0 Hz), 7.90 (1H, dd, J=8.8 and 0.7 Hz), 8.41 (1H, dd, J=3.0 and 0.7 Hz)

APCI-MASS: m/z=384 (M^++H)

Preparation 167

4-[4-(4-Phenylcyclohexyl)piperazin-1-yl]benzoic acid dihydrochloride

IR (KBr): 1700.9, 1606.4, 1220.7, 1180.2 cm^{-1}

NMR (DMSO-d_6, δ): 1.4–1.85 (4H, m), 1.9–2.05 (2H, m), 2.2–2.4 (2H, m), 3.1–3.5 (6H, m), 3.5–3.7 (2H, m), 3.9–4.2 (2H, m), 7.06 (2H, d, J=8.8 Hz), 7.1–7.4 (5H, m), 7.83 (2H, d, J=8.8 Hz)

APCI-MASS: m/z=365 (M^++H)

Preparation 168

4-(4-Trans-n-pentylcyclohexyl)benzoic acid

IR (KBr): 1681.6, 1423.2, 1290.1 cm^{-1}

NMR (DMSO-d_6, δ): 0.90 (3H, t, J=6.6 Hz), 1.0–1.6 (13H, m), 1.89 (4H, d, J=10 Hz), 2.54 (1H, t, J=12 Hz), 7.30 (2H, d, J=8.3 Hz), 8.03 (2H, d, J=8.3 Hz)

APCI-MASS: m/z=274 (M^++H)

Preparation 169

4-(4-Piperidinopiperidin-1-yl)benzoic acid

IR (KBr): 1710.6, 1403.9 cm^{-1}

NMR (DMSO-d_6, δ): 1.6–2.1 (8H, m) 2.17 (2H, d, J=12 Hz), 2.7–3.05 (4H, m), 3.2–3.5 (1H, m), 3.35 (2H, d, J=12 Hz), 4.05 (2H, d, J=13 Hz), 7.01 (2H, d, J=8.9 Hz), 7.77 (2H, d, J=8.9 Hz), 10.84 (1H, s)

APCI-MASS: m/z=289 (M^++H)

Preparation 170

3-Chloro-4-[4-(4-hexyloxyphenyl)piperazin-1-yl] benzoic acid dihydrochloride

IR (KBr): 1712.5, 1598.7, 1513.8, 1251.6 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.6 Hz), 1.2–1.5 (6H, m), 1.6–1.8 (2H, m), 3.4–3.6 (8H, m), 3.98 (2H, t, J=6.4 Hz), 7.02 (2H, d, J=9.0 Hz), 7.32 (1H, d, J=8.1 Hz), 7.60 (2H, d, J=9.0 Hz), 7.89 (1H, d, J=8.1 Hz), 8.02 (1H, s)

APCI-MASS: m/z=417 (M^++H)

The following compounds (Preparations 171 to 175) were obtained according to a similar manner to that of Preparation 41.

Preparation 171

Ethyl [4-(4-octylphenyl)-2,3-dihydro-4H-1,2,4triazole-3-one-2-yl]acetate

IR (KBr): 2921.6, 1764.5, 1715, 1197.6 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.7 Hz), 1.30 (3H, t, J=7.1 Hz), 1.2–1.4 (10H, m), 1.5–1.7 (2H, m), 2.63 (2H, t, J=7.9 Hz), 4.26 (2H, q, J=7.1 Hz), 4.64 (2H, s), 7.28 (2H, d, J=8.4 Hz), 7.44 (2H, d, J=8.4 Hz), 7.71 (1H, s)

Preparation 172

4-[4-(4-tert-Butoxycarbonylpiperazin-1-yl)phenyl]-2-(4-methylpentyl)-2,3-dihydro-4H-1,2,4-triazol-3-one

IR (KBr): 1687.4 cm^{-1}

NMR (DMSO-d_6, δ): 0.90 (6H, d, J=6.5 Hz), 1.1–1.4 (2H, m), 1.49 (9H, s), 1.4–1.9 (3H, m), 3.16 (4H, t, J=4.9 Hz), 3.59 (4H, t, J=4.9 Hz), 3.82 (2H, t, J=7.3 Hz), 6.98 (2H, d, J=9.0 Hz), 7.41 (2H, d, J=9.0 Hz), 7.61 (1H, s)

Preparation 173

Methyl 6-(8-bromooctyloxy)-2-naphthoate

IR (KBr): 2933.2, 2856.1, 1720.2, 1294, 1209.1 cm^{-1}

NMR (DMSO-d_6, δ): 1.3–1.6 (8H, m), 1.75–2.0 (4H, m), 3.42 (2H, t, J=6.8 Hz), 3.96 (3H, s), 4.09 (2H, t, J=6.5 Hz), 7.14 (1H, d, J=1.7 Hz), 7.19 (1H, dd, J=8.9 and 1.7 Hz), 7.73 (1H, d, J=8.7 Hz), 7.83 (1H, d, J=8.9 Hz), 8.01 (1H, dd, J=8.7 and 1.7 Hz), 8.51 (1H, d, J=1.7 Hz)

APCI-MASS: m/z=393 (M^++H)

Preparation 174

4-[4-(6-n-Propyloxyhexyloxy)phenyl]benzoic acid

IR (KBr): 2937, 2858, 1695, 1683, 1604, 1430, 1290, 1247, 1195 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=7.4 Hz), 1.3–1.9 (10H, m), 3.2–3.4 (4H, m), 4.01 (2H, t, J=6.3 Hz), 7.04 (2H, d, J=8.7 Hz), 7.67 (2H, d, J=8.7 Hz), 7.74 (2H, d, J=8.3 Hz), 7.98 (2H, d, J=8.3 Hz), 12.9 (1H, s)

APCI-MASS: m/z=357 ($M+H^+$)

Preparation 175

4-[4-(6-Bromohexyloxy)phenyl]bromobenzene

NMR (DMSO-d_6, δ): 1.40–1.65 (4H, m), 1.70–2.00 (4H, m), 3.43 (2H, t, J=6.7 Hz), 4.00 (2H, t, J=6.4 Hz), 6.95 (2H, d, J=8.8 Hz), 7.30–7.60 (6H, m)

The following compounds (Preparations 176 to 180) were obtained according to a similar manner to that of Preparation 43.

Preparation 176

4-[4-(4-n-Pentyloxyphenyl)piperazin-1-yl]benzoic acid dihydrochloride

IR (KBr): 1668.1, 1602.6, 1510.0, 1228.4 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (3H, t, J=6.9 Hz), 1.2–1.5 (5H, m), 1.6–1.9 (2H, m), 3.0–3.2 (4H, m), 3.4–3.6 (4H, m), 3.88 (2H, t, J=6.4 Hz), 6.83 (2H, d, J=9 Hz), 6.9–7.1 (4H, m), 7.79 (2H, d, J=8.8 Hz), 12.32 (1H, s)

APCI-MASS: m/z=369 ($M+H^+$)

Preparation 177

4-[4-(4-n-Heptyloxyphenyl)pipeerazin-1-yl]benzoic acid dihydrochloride

IR (KBr): 1666.2, 1600.6, 1511.9 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (3H, t, J=6.9 Hz), 1.2–2.0 (10H, m), 3.1–3.3 (4H, m), 3.4–3.6 (4H, m), 3.92 (2H, t, J=6.4 Hz), 6.8–7.1 (6H, m), 8.00 (2H, d, J=8.8 Hz)

Preparation 178

4-[4-[4-(4-Methylpentyloxy)phenyl]piperazine-1-yl] benzoic acid dihydrochloride

IR (KBr): 1668.1, 1602.6, 1510.0, 1236.1 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (6H, d, J=6.5 Hz), 1.2–1.4 (2H, m), 1.4–1.8 (3H, m), 3.0–3.2 (4H, m), 3.3–3.5 (4H, m), 3.87 (2H, t, J=6.3 Hz), 6.83 (2H, d, J=9.0 Hz), 6.9–7.1 (4H, m), 7.79 (2H, d, J=8.8 Hz), 12.33 (1H, s)

APCI-MASS: m/z=383 ($M+H^+$)

Preparation 179

4-[4-[4-(8-Bromooctyloxy)phenyl]piperazin-1-yl] benzoic acid dihydrochloride

IR (KBr): 1670.1, 1602.6, 1511.9, 1234.2 cm^{-1}

NMR (DMSO-d_6, δ): 1.2–1.5 (8H, m), 1.6–1.9 (4H, m), 3.0–3.2 (4H, m), 3.2–3.5 (4H, m), (2H, t, J=6.7 Hz), 3.88 (2H, t, J=6.4 Hz), 6.83 (2H, d, J=9.1 Hz), 6.94 (2H, d, J=9.1 Hz), 7.02 (2H, d, J=8.9 Hz), 7.79 (2H, d, J=8.9 Hz)

Preparation 180

3-Fluoro-4-[4-(4-n-hexyloxyphenyl)piperazin-1-yl] benzoic acid dihydrochloride

IR (KBr): 1673.9, 1511.9, 1240.0 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.5 Hz), 1.2–1.5 (6H, m), 1.6–1.8 (2H, m), 3.0–3.5 (8H, m), 3.88 (2H, t, J=6.4 Hz), 6.7–7.2 (5H, m), 7.4–7.8 (2H, m), 12.82 (1H, s)

APCI-MASS: m/z=401 (M^++H)

The following compound was obtained according to a similar manner to that of Preparation 46.

Preparation 181

1-(4-Methoxycarbonylphenyl)-3-(4-n-hexyloxyphenyl)-propan-1,3-dione

IR (KBr): 2956, 2927, 2856, 1722, 1511, 1284, 1108 cm^{-1}

NMR (DMSO-d_6, δ): 0.92 (3H, t, J=6.4 Hz), 1.2–2.0 (8H, m), 3.96 (3H, s), 4.04 (2H, t, J=6.5 Hz), 6.82 (1H, s), 6.97 (2H, d, J=8.7 Hz), 7.9–8.1 (4H, m), 8.14 (2H, d, J=8.3 Hz)

APCI-MASS: m/z=383 ($M+H^+$)

The following compounds (Preparations 182 to 185) were obtained according to a similar manner to that of Preparation 47.

Preparation 182

Methyl 5-(4-octyloxyphenyl)-1-methylpyrazole-3-carboxylate IR (KBr pelet): 2923, 1724, 1616, 1513, 1446, 1251, 1120 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (3H, t, J=6.8 Hz), 1.2–1.5 (10H, m), 1.7–1.9 (2H, m), 3.90 (3H, s), 3.98 (2H, t, J=6.6 Hz), 4.20 (3H, s), 6.92 (2H, d, J=8.9 Hz), 7.04 (1H, s), 7.89 (2H, d, J=8.9 Hz)

APCI-MASS: m/z=345 ($M+H^+$)

Preparation 183

Methyl 4-[5-(4-n-pentyloxyphenyl)pyrazol-3-yl] benzoate

IR (KBr): 3236, 2952, 2873, 1716, 1616, 1508, 1276, 1174, 1106 cm^{-1}

NMR (DMSO-d_6, δ): 0.94 (3H, t, J=7.0 Hz), 1.3–1.5 (4H, m), 1.7–1.9 (2H, m), 3.92 (3H, s), 3.96 (2H, t, J=6.7 Hz), 6.78 (1H, s), 6.88 (2H, d, J=8.7 Hz), 7.55 (2H, d, J=8.7 Hz), 7.79 (2H, d, J=8.4 Hz), 8.02 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=365 ($M+H^+$)

Preparation 184

Methyl 5-(4-octyloxyphenyl)isoxazole-3-carboxylate

IR (KBr pelet): 2950, 2921, 1724, 1614, 1510, 1446, 1257, 1178, 1143, 1009 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.8 Hz), 1.2–1.6 (10H, m), 1.7–1.9 (2H, m), 4.0–4.1 (5H, m), 6.80 (1H, s), 6.98 (2H, dd, J=6.9 and 2.1 Hz), 7.73 (2H, dd, J=6.9 and 2.1 Hz)

APCI-MASS: m/z=332 ($M+H^+$)

Preparation 185

Methyl 4-[3-(4-n-hexyloxyphenyl)pyrazol-5-yl] benzoate

IR (KBr): 2952, 1716, 1616, 1508, 1276, 1106 cm^{-1}

NMR ($CDCl_3$, δ): 0.91 (3H, t, J=6.3 Hz), 1.2–1.6 (6H, m), 1.7–1.9 (2H, m), 3.8–4.0 (5H, m), 6.76 (1H, s), 6.86 (2H, d, J=8.8 Hz), 7.54 (2H, d, J=8.8 Hz), 7.77 (2H, d, J=8.4 Hz), 8.00 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=379 ($M+H^+$)

Preparation 186

A suspension of 1-(4-n-Pentyloxyphenyl)-3-(4-ethoxycarbonylphenyl)-1-buten-3-one (74.43 g) and hydroxyamine hydrochloride (28.23 g) and potassium carbonate (56.11 g) in ethanol (400 ml) was refluxed for 4 hours. The mixture was diluted with ethyl acetate, washed with water (×2), brine and dried over magnesium sulfate. The solvents were removed under reduced pressure to give crude oxime. To a solution of crude oxime in dichloroethane (500 ml) was added activated-manganese (IV) oxide (200 g). The reaction mixture was refluxed for 2 hours and filtered. The residue was washed with dichloromethane. The solvents were removed under reduced pressure and the residue was triturated with acetonitrile. The solid was collected by filtration and dried to give ethyl 4-[5-(4-n-Pentyloxyphenyl) isoxazol-3-yl]benzoate (21.07 g).

IR (KBr): 2945, 2872, 1717, 1615, 1508, 1280, 1108 cm^{-1}

NMR ($CDCl_3$, δ): 0.95 (3H, t, J=6.9 Hz), 1.3–1.9 (9H, m), 4.01 (2H, t, J=6.5 Hz), 4.41 (2H, q, J=7.1 Hz), 6.74 (1H, s), 6.99 (2H, d, J=8.8 Hz), 7.76 (2H, d, J=8.8 Hz), 7.93 (2H, d, J=8.4 Hz), 8.15 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=380 ($M+H^+$)

The following compounds (Preparations 187 to 190) were obtained according to a similar manner to that of Preparation 48.

Preparation 187

Methyl 6-[4-[4-(8-Methoxyoctyloxy)phenyl] piperazin-1-yl]nicotinate

IR (KBr): 2933, 2858, 1722, 1608, 1513, 1432, 1405, 1278, 1245 cm^{-1}

NMR ($CDCl_3$, δ): 1.3–1.9 (12H, m), 3.16 (4H, t, J=5.0 Hz), 3.33 (3H, s), 3.36 (2H, t, J=6.5 Hz), 3.8–4.0 (9H, m), 6.64 (1H, d, J=9.1 Hz), 6.85 (2H, d, J=9.2 Hz), 6.93 (2H, d, J=9.2 Hz), 8.04 (1H, dd, J=9.1 and 2.2 Hz), 8.81 (1H, d, J=2.2 Hz)

APCI-MASS: m/z=456 ($M+H^+$)

Preparation 188

4-[4-(5-Methoxypentyloxy)phenyl]bromobenzene

IR (KBr): 2940, 2856, 1604, 1479, 1286, 1255, 1124 cm^{-1}

NMR ($CDCl_3$, δ): 1.5–1.9 (6H, m), 3.34 (3H, s), 3.41 (2H, t, J=6.1 Hz), 3.99 (2H, t, J=6.4 Hz), 6.95 (2H, d, J=8.7 Hz), 7.4–7.6 (6H, m)

APCI-MASS: m/z=349 ($M+H^+$)

Preparation 189

Methyl 6-(8-methoxyoctyloxy)-2-naphthoate

NMR ($CDCl_3$, δ): 1.2–1.6 (10H, m), 1.7–1.9 (2H, m), 3.20 (3H, s), 3.29 (2H, t, J=6.4 Hz), 3.89 (3H, s), 4.11 (2H, t, J=6.4 Hz), 7.24 (1H, dd, J=9.0 and 2.4 Hz), 7.40 (1H, d, J=2.4 Hz), 7.88 (1H, d, J=8.7 Hz), 7.94 (1H, dd, J=8.7 and 1.5 Hz), 8.03 (1H, d, J=9.0 Hz), 8.55 (1H, d, J=1.5 Hz)

Preparation 190

4-[4-[4-(8-Methoxyoctyloxy)phenyl]piperazin-1-yl] benzoic acid dihydrochloride

IR (KBr): 1668.1, 1602.6, 1511.9, 1236.1 cm^{-1}

NMR ($CDCl_3$, δ): 1.2–1.8 (12H, m), 3.05–3.2 (4H, m), 3.29 (2H, t, J=7.1 Hz), 3.33 (3H, s), 3.4–3.55 (4H, m), 3.88 (2H, t, J=6.4 Hz), 6.82 (2H, d, J=9.0 Hz), 6.94 (2H, d, J=9.0 Hz), 7.02 (2H, d, J=8.8 Hz), 7.79 (2H, d, J=8.8 Hz), 12.31 (1H, s)

The following compounds (Preparation 191 to 254) were obtained according to a similar manner to that of Preparation 49.

Preparation 191

1-[4-[4-[4-[2-(4-Methylpentyl)-2,3-dihydro-4H-1,2,4-triazol-3-one-4-yl]phenyl]piperazin-1-yl]benzoyl] benzotriazole 3-oxide

IR (KBr): 1766.5, 1693.2, 1600.6, 1519.6 cm^{-1}

Preparation 192

1-[4-(4-Octylphenyl)-2,3-dihydro-4H-1,2,4-triazol-3-one-2-yl-acetyl]benzotriazole 3-oxide

IR (KBr): 2921.6, 1753.0, 1720.0, 1423.2 cm^{-1}

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.7 Hz), 1.2–1.4 (10H, m), 1.5–1.8 (2H, m), 2.65 (2H, t, J=7.5 Hz), 5.46 (2H, s), 7.30 (2H, d, J=8.5 Hz), 7.48 (2H, d, J=8.5 Hz), 7.62 (1H, t, J=8.3 Hz), 7.80 (1H, s), 7.82 (1H, t, J=8.3 Hz), 8.05 (1H, d, J=8.3 Hz), 8.37 (1H, d, J=8.3 Hz)

Preparation 193

1-[4-[4-[4-(7-Methoxyheptyloxy)phenyl]piperazin-1-yl]benzoyl]benzotriazole 3-oxide

IR (KBr): 1783.8, 1600.6, 1511.9, 1232.3, 1184.1 cm^{-1}

NMR ($CDCl_3$, δ): 1.3–1.9 (10H, m), 3.2–3.3 (4H, m), 3.34 (3H, s), 3.38 (2H, t, J=6.4 Hz), 3.5–3.7 (4H, m), 3.92 (2H, t, J=6.5 Hz), 6.87 (2H, d, J=9.2 Hz), 6.95 (2H, d, J=9.2 Hz), 7.00 (2H, d, J=9.0 Hz), 7.3–7.6 (3H, m), 8.09 (1H, d, J=8.2 Hz), 8.15 (2H, d, J=9.0 Hz)

Preparation 194

1-[4-[4-(4-n-Heptyloxyphenyl)piperazin-1-yl] benzoyl]benzotriazole 3-oxide

IR (KBr): 1783.8, 1600.6, 1511.9, 1230.4, 1184.1 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.3 Hz), 1.2–1.6 (8H, m), 1.7–1.9 (2H, m), 3.2–3.3 (4H, m), 3.5–3.7 (4H, m), 1.7–1.9 (2H, m), 3.2–3.3 (4H, m), 3.5–3.7 (4H, m), 3.93 (2H, t, J=6.5 Hz), 6.87 (2H, d, J=9.2H), 6.95 (2H, d, J=9.2 Hz), 7.00 (2H, d, J=9.0 Hz), 7.3–7.7 (3H, m), 8.09 (1H, d, J=8.2 Hz), 8.15 (2H, d, J=9.0 Hz)

Preparation 195

1-[4-[4-[4-(4-Methylpentyloxy)phenyl]piperazin-1-yl]-benzoyl]benzotriazole 3-oxide

NMR ($CDCl_3$, δ): 0.92 (6H, d, J=6.6 Hz), 1.2–1.4 (2H, m), 1.5–1.9 (3H, m), 3.1–3.3 (4H, m), 3.5–3.7 (4H, m), 3.92

(2H, t, J=6.6 Hz), 6.87 (2H, d, J=9.3 Hz), 6.96 (2H, d, J=9.3 Hz), 7.01 (2H, d, J=9.0 Hz), 7.4–7.6 (3H, m), 8.10 (1H, d, J=8.2 Hz), 8.15 (2H, d, J=9.0 Hz)

Preparation 196

1-[4-[4-(4-n-Pentyloxyphenyl)piperazin-1-yl] benzoyl]benzotriazole 3-oxide

IR (KBr): 1787.7, 1600.6, 1511.9, 1232.3, 1184.1 cm^{-1}

NMR ($CDCl_3$, δ): 0.93 (3H, t, J=6.9 Hz), 1.3–1.6 (4H, m, 1.7–1.9 (2H, m), 3.1–3.4 (4H, m), 3.5–3.8 (4H, m), 3.93 (2H, t, J=6.6 Hz), 6.87 (2H, d, J=9.2 Hz), 6.92 (2H, d, J=9.2 Hz), 7.01 (2H, d, J=9.1 Hz), 7.4–7.6 (3H, m), 8.10 (1H, d, J=8.2 Hz), 8.15 (2H, d, J=9.1 Hz)

Preparation 197

1-[4-[4-[8-(1H-Tetrazol-1-yl)octyloxy]phenyl] benzoyl]benzotriazole 3-oxide and

1-[4-[4-[8-(2H-tetrazol-2-yl)octyloxy]phenyl] benzoyl]benzotriazole 3-oxide

IR (KBr): 1778.0, 1602.6, 1189.9, 981.6 cm^{-1}

NMR ($CDCl_3$, δ): 1.2–1.6 (8H, m), 1.7–1.9 (2H, m), 1.9–2.2 (2H, m), 4.02 (2H, t, J=6.4 Hz), 4.44 and 4.66 (2H, t, J=7.1 Hz), 7.02 (2H, d, J=8.8 Hz), 7.4–7.6 (3H, m), 7.63 (2H, d, J=8.8 Hz), 7.79 (2H, d, J=8.6 Hz), 8.12 (1H, d, J=8.2 Hz), 8.32 (2H, d, J=8.6 Hz), 8.51 and 8.60 (1H, s)

Preparation 198

1-[4-[4-[8-(2,6-Dimethylmorpholin-4-yl)octyloxy] phenyl]benzoyl]benzotriazole 3-oxide

IR (KBr): 1778.0, 1600.6, 977.7 cm^{-1}

NMR ($CDCl_3$, δ): 1.18 (6H, d, J=6.3 Hz), 1.2–1.7 (10H, m), 1.7–2.0 (4H, m), 2.4–2.6 (2H, m), 2.9–3.2 (2H, m), 3.7–3.9 (2H, m), 4.01 (2H, t, J=6.5 Hz), 7.02 (2H, d, J=8.8 Hz), 7.4–7.7 (3H, m), 7.63 (2H, d, J=8.8 Hz), 7.79 (2H, d, J=8.5 Hz), 8.12 (1H, d, J=8.1 Hz), 8.32 (2H, d, J=8.5 Hz)

Preparation 199

1-[6-[4-(4-Octyloxyphenyl)piperazin-1-yl] nicotinoyl]benzotriazole 3-oxide

IR (KBr pelet): 2922, 2854, 1766, 1602, 1513, 1417, 1234, 1025, 950, 813 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.8 Hz), 1.2–1.5 (10H, m), 1.7–1.9 (2H, m), 3.1–3.3 (4H, m), 3.9–4.1 (6H, m), 6.75 (1H, d, J=9.2 Hz), 6.87 (2H, d, J=9.2 Hz), 6.95 (2H, d, J=9.2 Hz), 7.4–7.6 (3H, m), 8.10 (1H, d, J=8.1 Hz), 8.19 (1H, dd, J=9.2 and 2.4 Hz), 9.04 (1H, d, J=2.4 Hz)

APCI-MASS: m/z=529 $(M+H^+)$

Preparation 200

1-[2-(4-Hexyloxyphenyl)benzoxazol-5-yl-carbonyl] benzotriazole 3-oxide

IR (KBr): 2950, 1774, 1623, 1504, 1265, 1176 cm^{-1}

NMR ($CDCl_3$, δ): 0.93 (3H, t, J=6.9 Hz), 1.3–1.6 (6H, m), 1.8–2.0 (2H, m), 4.07 (2H, t, J=6.5 Hz), 7.06 (2H, d, J=8.9 Hz), 7.4–7.6 (3H, m), 7.75 (1H, d, J=8.6 Hz), 8.13 (1H, d, J=8.2 Hz), 8.2–8.4 (3H, m), 8.67 (1H, d, J=1.6 Hz)

APCI-MASS: m/z=457 $(M+H^+)$

Preparation 201

1-[4-[4-(4-n-Butyloxyphenyl)phenyl]benzoyl] benzotriazole 3-oxide

IR (KBr): 2958, 2871, 1776, 1600, 1398, 1255, 1211, 1037 cm^{-1}

NMR ($CDCl_3$, δ): 1.00 (3H, t, J=7.2 Hz), 1.4–1.9 (4H, m), 4.03 (2H, t, J=6.4 Hz), 7.01 (2H, d, J=8.3 Hz), 7.4–7.8 (9H, m), 7.87 (2H, d, J=8.1 Hz), 8.12 (1H, d, J=8.4 Hz), 8.36 (2H, d, J=7.9 Hz)

APCI-MASS: m/z=464 $(M+H)^+$

Preparation 202

1-[2-(4-Heptyloxyphenyl)pyridin-5-yl-carbonyl] benzotriazole 3-oxide

IR (KBr): 2944, 2867, 1793, 1770, 1589, 1471, 1321, 1093 cm^{-1}

NMR ($CDCl_3$, δ): 0.91 (3H, t, J=6.7 Hz), 1.2–1.6 (8H, m), 1.7–1.9 (2H, m), 4.05 (2H, t, J=6.5 Hz), 7.04 (2H, d, J=8.0 Hz), 7.4–7.6 (3H, m), 7.91 (1H, d, J=8.5 Hz), 8.1–8.2 (3H, m), 8.51 (1H, dd, J=8.5 and 2.3 Hz), 9.47 (1H, d, J=2.3 Hz)

APCI-MASS: m/z=431 $(M+H^+)$

Preparation 203

1-[2-(2-Octyloxypyridin-5-yl)benzoxazol-5-yl-carbonyl]benzotriazole 3-oxide

IR (KBr pelet): 2925, 2854, 1787, 1623, 1479, 1263, 989 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.8 Hz), 1.2–1.5 (10H, m), 1.8–1.9 (2H, m), 4.42 (2H, t, J=6.7 Hz), 6.91 (1H, d, J=8.7 Hz), 6.4–6.6 (3H, m), 7.79 (1H, d, J=8.6 Hz), 8.13 (1H, d, J=8.2 Hz), 8.32 (1H, dd, J=8.6 and 1.7 Hz), 8.41 (1H, dd, J=8.7 and 2.4 Hz), 8.70 (1H, d, J=1.4 Hz), 9.07 (1H, d, J=1.9 Hz)

APCI-MASS: m/z=486 $(M+H^+)$

Preparation 204

1-[2-[4-(4-Hexylphenyl)phenyl]benzoxazol-5-yl-carbonyl]benzotriazole 3-oxide

IR (KBr): 2927, 2854, 1785, 1621,1490, 1261, 1166, 1052 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.5 Hz), 1.2–1.8 (8H, m), 2.68 (2H, t, J=7.9 Hz), 7.31 (2H, d, J=8.2 Hz), 7.4–7.7 (5H, m), 7.79–7.81 (3H, m), 8.13 (1H, d, J=8.3 Hz), 8.3–8.4 (3H, m), 8.73 (1H, d, J=1.3 Hz)

APCI-MASS: m/z=517 $(M+H^+)$

Preparation 205

1-[2-[4-(4-n-Butyloxyphenyl)phenyl]pyridin-5-yl-carbonyl]benzotriazole 3-oxide

IR (KBr): 2956, 2933, 2871, 1774, 1650, 1591, 1471, 1251 cm^{-1}

NMR ($CDCl_3$, δ): 1.00 (3H, t, J=7.2 Hz), 1.5–1.9 (4H, m), 4.03 (2H, t, J=6.4 Hz), 7.02 (2H, d, J=8.6 Hz), 7.4–7.6 (3H, m), 7.54 (2H, d, J=7.3 Hz), 7.62 (2H, d, J=8.5 Hz), 8.02 (1H, d, J=8.3 Hz), 8.13 (1H, d, J=8.2 Hz), 8.21 (2H, d, J=7.9 Hz), 8.57 (1H, dd, J=8.3 and 2.0 Hz), 9.54 (1H, d, J=2.0 Hz)

APCI-MASS: m/z=465 $(M+H)^+$

Preparation 206

1-[4-[4-(5-Phenoxypentyloxy)phenyl]benzoyl]-benzotriazole 3-oxide

IR (KBr): 2944, 2869, 1770, 1600, 1494, 1249, 1189 cm^{-1}

NMR ($CDCl_3$, δ): 1.6–1.8 (2H, m), 1.8–2.0 (4H, m), 4.01 (2H, t, J=6.3 Hz), 4.07 (2H, t, J=6.2 Hz), 6.91 (2H, d, J=8.9

Hz), 7.04 (2H, d, J=8.7 Hz), 7.3–7.6 (4H, m), 7.63 (2H, d, J=8.6 Hz), 7.78 (2H, d, J=8.4 Hz), 8.12 (1H, d, J=8.1 Hz), 8.32 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=494 $(M+H)^+$

Preparation 207

1-[4-[5-(4-Hexyloxyphenyl)1,3,4-oxadiazol-2-yl] benzoyl]benzotriazole 3-oxide

IR (KBr): 2956, 2921, 2856, 1778, 1612, 1496, 1261, 1232, 1025 cm^{-1}

NMR ($CDCl_3$, δ): 0.92 (3H, t, J=6.7 Hz), 1.3–1.6 (6H, m), 1.8–2.0 (2H, m), 4.05 (2H, t, J=6.5 Hz), 7.05 (2H, d, J=8.7 Hz), 7.4–7.6 (3H, m), 8.10 (2H, d, J=8.7 Hz), 8.13 (1H, d, J=7.4 Hz), 8.37 (2H, d, J=8.5 Hz), 8.45 (2H, d, J=8.5 Hz)

APCI-MASS: m/z=484 $(M+H)^+$

Preparation 208

1-[4-[5-(4-n-Hexyloxyphenyl)-1,3,4-thiadiazol-2-yl] benzoyl]benzotriazole 3-oxide

IR (KBr): 2952, 2873, 1774, 1602, 1261, 1230, 1176 cm^{-1}

NMR ($CDCl_3$, δ): 0.93 (3H, t, J=6.8 Hz), 1.3–2.0 (8H, m), 4.04 (2H, t, J=6.5 Hz), 7.02 (2H, d, J=8.7 Hz), 7.4–7.7 (3H, m), 7.98 (2H, d, J=8.7 Hz), 8.13 (1H, d, J=8.7 Hz), 8.25 (2H, d, J=8.3 Hz), 8.41 (2H, d, J=8.3 Hz)

APCI-MASS: m/z=500 $(M+H)^+$

Preparation 209

1-[5-(4-Octyloxyphenyl)-1-methylpyrazol-3-yl-carbonyl]benzotriazole 3-oxide

IR (KBr pelet): 2939, 2852, 1776, 1687, 1612, 1448, 1249, 995 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.7 Hz), 1.3–1.5 (10H, m), 1.7–1.9 (2H, m), 4.01 (2H, t, J=6.5 Hz), 4.25 (3H, s), 6.97 (2H, d, J=6.8 Hz), 7.4–7.7 (4H, m), 7.78 (2H, d, J=6.8 Hz), 8.14 (1H, d, J=8.0 Hz)

APCI-MASS: m/z=448 $(M+H^+)$

Preparation 210

1-[4-[5-(4-n-Pentyloxyphenyl)pyrazol-3-yl]benzoyl] benzotriazole 3-oxide

IR (KBr): 3251, 2956, 2869, 1780, 1612, 1506, 1232, 985 cm^{-1}

NMR ($CDCl_3$, δ): 0.95 (3H, t, J=6.9 Hz), 1.3–1.6 (4H, m), 1.7–2.0 (2H, m), 4.01 (2H, t, J=6.6 Hz), 6.90 (1H, s), 6.99 (2H, d, J=8.7 Hz), 7.4–7.6 (5H, m), 8.0–8.2 (3H, m), 8.33 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=468 $(M+H^+)$

Preparation 211

1-[5-[4-(4-n-Butoxyphenyl)phenyl]furan-2-yl-carbonyl]benzotriazole 3-oxide

IR (KBr): 2958, 2871, 1781, 1678, 1603, 1535, 1479, 1265 cm^{-1}

NMR ($CDCl_3$, δ): 1.00 (3H, t, J=7.3 Hz), 1.4–1.9 (4H, m), 4.02 (2H, t, J=6.4 Hz), 6.9–7.1 (3H, m), 7.4–8.2 (11H, m)

APCI-MASS: m/z=351 (Methyl ester)

Preparation 212

1-(3-(S)-Hydroxy-2-benzylhexadecanoyl) benzotriazole 3-oxide

IR (Neat): 2854.1, 1814.7, 1459.8, 742.5 cm^{-1}

Preparation 213

1-(3-(R)-Benzyloxycarboxylamino-18 -methoxyoctadecanoyl)-benzotriazole 3-oxide

IR (KBr): 1805.0, 1729.8, 1695.1 cm^{-1}

NMR ($CDCl_3$, δ): 1.1–1.65 (30H, m), 3.20 (3H, s), 3.28 (2H, t, J=6.5 Hz), 4.01 (1H, m), 5.06 (2H, s), 7.32 (5H, m), 7.4–7.8 (3H, m), 8.12 (1H, d, J=7 Hz)

Preparation 214

1-(3-(S)-Hydroxyhexadecanoyl)benzotriazole 3-oxide

IR (KBr): 1710.6, 1498.4, 1429.0, 771.4 cm^{-1}

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.4 Hz), 1.2–1.7 (24H, m), 2.00 (1H, s), 3.1–3.5 (2H, m), 4.30 (1H, m), 7.59 (1H, t, J=7.8 Hz), 7.81 (1H, t, J=7.8 Hz), 8.02 (1H, d, J=8.3 Hz), 8.42 l(1H, d, J=8.3 Hz)

Preparation 215

1-(3-Methyl-2-tridecenoyl)benzotriazole 3-oxide

IR (KBr): 2927.4, 1791.5, 1633.4, 1081.9 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.3 Hz), 1.1–1.7 (20H, m), 2.25 (3H, s), 6.08 (1H, s), 7.3–7.6 (3H, m), 8.06 (1H, d, J=8.2 Hz)

Preparation 216

1-[4-[4-[4-(8-Methoxyoctyloxy)phenyl]piperazin-1-yl]benzoyl]benzotriazole 3-oxide

IR (KBr): 1780.0, 1600.6, 1511.9, 1234.2, 1184.1 cm^{-1}

NMR ($CDCl_3$, δ): 1.3–1.9 (12H, m), 3.24 (4H, t, J=5.0 Hz), 3.33 (3H, s), 3.37 (2H, t, J=6.8 Hz), 3.62 (4H, t, J=5.0 Hz), 3.92 (2H, t, J=6.5 Hz), 6.8–7.1 (6H, m), 7.35–7.65 (3H, m), 8.09 (1H, d, J=8.2 Hz), 8.15 (2H, d, J=9.0 Hz)

Preparation 217

1-[3-Fluoro-4-[4-(4-n-hexyloxyphenyl)piperazin-1-yl]benzoyl]benzotriazole 3-oxide

IR (KBr): 1778.0 cm^{-1}

Preparation 218

1-[3-Chloro-4-[4-(4-n-hexyloxyphenyl)piperazin-1-yl]benzoyl]benzotriazole 3-oxide

IR (KBr): 1778.0, 1594.8, 1511.9, 1218.8 cm^{-1}

NMR ($CDCl_3$, δ): 0.91 (3H, t, J=6.5 Hz), 1.2–1.6 (6H, m), 1.6–1.9 (2H, m), 3.29 (4H, t, J=3.6 Hz), 3.44 (4H, t, J=3.6 Hz), 3.93 (2H, t, J=6.5 Hz), 6.87 (2H, d, J=9.2 Hz), 6.97 (2H, d, J=9.2 Hz), 7.19 (1H, d, J=8.6 Hz), 7.4–7.7 (3H, m), 8.10 (1H, d, J=6.4 Hz), 8.14 (1H, dd, J=8.6 and 2.1 Hz), 8.27 (1H, d, J=2.1 Hz)

APCI-MASS: m/z=534 $(M^+ + H)$

Preparation 219

1-[4-(4-Piperidinopiperidin-1-yl)benzoyl] benzotriazole 3-oxide

IR (KBr): 1758.8, 1602.6, 1186.0 cm^{-1}

NMR ($CDCl_3$, δ): 1.35–1.8 (8H, m), 1.96 (2H, d, J=13 Hz), 2.45–2.7 (5H, m), 2.97 (2H, td, J=12.8 and 2.6 Hz),

4.04 (2H, d, J=13 Hz), 6.93 (2H, d, J=9.2 Hz), 7.35–7.6 (3H, m), 8.1–8.4 (3H, m).

Preparation 220

1-[3-[4-(4-n-Hexyloxyphenyl)piperazin-1-yl] pyridazin-6-yl-carbonyl]benzotriazole 3-oxide

IR (KBr): 1787.7, 1585.2, 1511.9, 1240.0 cm^{-1}

Preparation 221

1-[5-[4-(4-n-Hexyloxyphenyl)piperazin-1-yl] picolinoyl]-benzotriazole 3-oxide

IR (KBr): 1766.5, 1575.6, 1511.9, 1232.3 cm^{-1}

NMR ($CDCl_3$, δ): 0.91 (3H, t, J=6.5 Hz), 1.2–1.6 (6H, m), 1.65–1.9 (2H, m), 3.27 (4H, t, J=5.1 Hz), 3.66 (4H, t, J=5.1 Hz), 3.93 (2H, t, J=6.5 Hz), 6.88 (2H, d, J=9.2 Hz), 6.95 (2H, d, J=9.2 Hz), 7.25 (1H, dd, J=7.6 and 2.9 Hz), 7.35–7.6 (3H, m), 8.09 (1H, , d, J=8.2 Hz), 8.18 (1H, d, J=8.9 Hz), 8.52 (1H, d, J=2.9 Hz)

APCI-MASS: m/z=501 (M^++H)

Preparation 222

1-[4-[4-(4-Cyclohexylphenyl)piperazin-1-yl] benzoyl]-benzotriazole 3-oxide

IR (KBr): 1770.3, 1602.6, 1,515.8, 1186.0 cm^{-1}

NMR ($CDCl_3$, δ): 1.5–1.5 (6H, m), 1.65–2.0 (4H, m), 2.45 (1H, m), 3.33 (4H, t, J=5.1 Hz), 3.62 (4H, t, J=5.1 Hz), 6.92 (2H, d, J=8.7 Hz), 6.99 (2H, d, J=9.2 Hz), 7.16 (2H, d, J=8.7 Hz), 7.35–7.65 (3H, m), 8.09 (1H, d, J=8.2 Hz), 8.15 (2H, d, J=9.2 Hz)

Preparation 223

1-[4-[4-(4-n-Hexylphenyl)piperazin-1-yl]benzoyl] benzotriazole 3-oxide

IR (KBr): 1768.4, 1602.6, 15,15.8, 1230.4, 1184.1 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.5 Hz), 1.2–1.45 (6H, m), 1.5–1.7 (2H, m), 2.55 (2H, t, J=7.6 Hz), 3.2–3.4 (4H, m), 3.5–3.7 (4H, m), 6.91 (2H, d, J=8.6 Hz), 7.00 (2H, d, J=9.1 Hz), 7.13 (2H, d, J=8.5 Hz), 7.35–7.6 (3H, m), 8.09 (1H, d, J=8.2 Hz), 8.15 (2H, d, J=9.1 Hz)

Preparation 224

1-[4-[4-(4-Phenylcyclohexyl)piperazin-1-yl]benzoyl] benzotriazole 3-oxide

IR (KBr): 1780.0, 1762.6, 1602.6, 1234.2, 1182.2 cm^{-1}

NMR ($CDCl_3$, δ) (4H, m), 1.95–2.15 (4H, m), 2.35–2.6 (2H, m), 2.79 (4H, t, J=5.0 Hz), 3.49 (4H, t, J=5.0 Hz), 6.95 (2H, d, J=9.0 Hz), 7.1–7.35 (5H, m), 7.35–7.6 (3H, m), 8.08 (1H, d, J=7.1 Hz), 8.12(2H, d, J=9.0 Hz)

Preparation 225

1-[4-[4-[1-(4-n-Hexyloxyphenyl)piperidin-4-yl] piperazin-1-yl]benzoyl]benzotriazole 3-oxide

IR (KBr): 1768.4, 1602.6, 1511.9, 1234.2 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.5 Hz), 1.2–1.55 (6H, m), 1.6–1.9 (4H, m), 1.96 (2H, d, J=11 Hz), 2.44 (1H, m), 2.64 (2H, d, J=1.1 Hz), 2.77 (4H, t, J=5.0 Hz), 3.48 (4H, t, J=5.0 Hz), 3.59 (2H, d, J=11 Hz), 3.91 (2H, t, J=6.5 Hz), 6.7–7.05 (6H, m), 7.35–7.6 (3H, m), 8.08 (1H, d, J=6.9 Hz), 8.12 (2H, d, J=7.7 Hz)

Preparation 226

1-[4-(4-Trans-n-pentylcyclohexyl)benzoyl] benzotriazole 3-oxide

IR (KBr): 1799.3, 1778.0, 1608.3, 1228.4, 977.7 cm^{-}

NMR ($CDCl_3$, δ) 0.91 (3H, t, J=6.6 Hz), 1.0–1.7 (13H, m), 1.93 (4H, d, J=9.8 Hz), 2.62 (1H, t, J=12 Hz), 7.35–7.6 (5H, m), 8.09 (1H, d, J=7.9 Hz), 8.19 (2H, d, J=8.4 Hz)

Preparation 227

1-[6-(8-Methoxyoctyloxy)-2-naphthoyl] benzotriazole 3-oxide

IR (KBr): 2931.3, 2856.1, 1778.0, 1623.8 cm^{-1}

Preparation 228

1-(E)-[3-[4-[4-(7-Fluoroheptyloxy)phenyl]phenyl]-acryloyl]benzotriazole 3-oxide

IR (KBr): 3070.1, 2935.1, 2859.9, 1700.9, 1619.9, 1596.8 cm^{-1}

NMR ($CDCl_3$, δ): 1.30–2.00 (10H, m), 4.02 (2H, t; J=6.4 Hz), 4.45 (2H, dt, J=47.5 and 6.2 Hz), 6.70–8.65 (14H, m)

Preparation 229

1-(6-Heptylnaphthalene-2-carbonyl)benzotriazole 3-oxide

NMR (DMSO-d_6, δ): 0.75–6.93 (3H, m), 1.10–1.45 (8H, m), 1.55–1.80 (2H, m), 2.68–2.90 (2H, m), 7.35–9.06 (10H, m)

APCI-MASS: m/z=388 (M^++1)

Preparation 230

1-(E)-[3-[4-[4-(8-Methoxyoctyloxy)phenyl]phenyl]-acryloyl]benzotriazole 3-oxide

Preparation 231

1-(E)-[3-[4-[4-(5-Hexenyloxy)phenyl]phenyl] acryloyl]-benzotriazole 3-oxide

IR (KBr): 3072.0, 3033.5, 2939.0, 2865.7, 1780.0, 1693.2, 1619.9, 1596.8 cm^{-1}

NMR (DMSO-d_6, δ): 1.43–1.66 (2H, m), 1.66–1.90 (2H, m), 2.02–2.23 (2H, m), 3.90–4.16 (2H, m), 4.90–5.13 (2H, m), 5.72–6.00 (1H, m), 6.93–8.30 (14H, m)

APCI-MASS: m/z=337 (Methyl ester, M^++1)

Preparation 232

1-(E)-[3-[4-[4-(4-Methylpentyloxy)phenyl]phenyl] acryloyl]benzotriazole 3-oxide

IR (KBr): 3072.0, 3033.5, 2952.5, 2869.6, 1780.0, 1693.2, 1618.0, 1598.7 cm^{-1}

NMR (DMSO-d_6, δ) 0.90 (6H, d, J=6.5 Hz), 1.20–1.40 (2H, m), 1.50–1.90 (3H, m), 3.90–4.10 (2H, m), 6.40–8.30 (14H, m)

APCI-MASS: m/z=442 (M^++1)

Preparation 233

1-(E)-[3-[4-[4-(6-Fluorohexyloxy)phenyl]phenyl] acryloyl]benzotriazole 3-oxide

IR (KBr): 3074.0, 3033.5, 2939.0, 2865.7, 1780.0 1697.1, 1598.7 cm^{-1}

NMR (DMSO-d_6, δ) 1.25–1.83 (6H, m), 4.04 (2H, t, J=6.5 Hz), 4.45 (2H, dt, J=47.5 and 6.5 Hz), 6.9–8.3 (14H, m)

APCI-MASS: m/z=460 (M^++1)

Preparation 234

1-(E)-[3-[4-[4-(6-Methoxyhexyloxy)phenyl]phenyl] acryloyl]benzotriazole 3-oxide

NMR (DMSO-d_6, δ): 1.30–1.65 (6H, m), 1.65–1.90 (2H, m), 3.22 (3H, s), 3.22–3.40 (2H, m), 4.02 (2H, t, J=6.5 Hz), 6.5–8.3 (14H, m)

Preparation 235

1-[4-[3-(4-n-Hexyloxyphenyl)pyrazol-5-yl]benzoyl] benzotriazole 3-oxide

IR (KBr): 2935, 1780, 1610, 1506 1249, 1232, 1178, 1087 cm^{-1}

NMR ($CDCl_3$, δ) 0.91 OH, d, J=6.4 Hz), 1.2–1.6 (6H, m), 1.7–1.9 (2H, m), 3.98 (2H, t, J=6.5 Hz), 6.8–7.0 (3H, m), 7.4–7.6 (5H, m), 8.00 (2H, d, J=8.4 Hz), 8.10 (1H, d, J=8.1 Hz), 8.28 (1H, d, J=8.4 Hz)

APCI-MASS: m/z=482 ($M+H^+$)

Preparation 236

1-[4-[4-[4-(6-Methoxyhexyloxy)phenyl]phenyl] benzoyl]-benzotriazole 3-oxide

IR (KBr): 2.935, 2858, 1774, 1600, 1490, 1257, 1211 cm^{-1}

NMR ($CDCl_3$, δ) 1.4–1.9 (8H, m), 3.35 (3H, s), 340 (2H, t, J=6.3 Hz), 4.02 (21H, t, J=6.4 Hz) 7.00 (2H, d, J=8.7 Hz), 7.4–7.8 (7H, m), 7.87 (2H, d; J=8.4 Hz), 8.12 (1H, d, J=8.2 Hz), 8.36 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=522 ($M+H^+$)

Preparation 237

1-[4-[5-[4-(8-Methoxyoctyloxy)phenyl]-1,3,4-thiadiazol, 2-yl]benzoyl]benzotriazole 3-oxide

IR (KBr): 2929, 2854, 1776, 1602, 1469, 1255 cm^{-1}

NMR ($CDCl_3$, δ) 1.2–1.6 (10H, m), 1.7–1.9 (2H, m), 3.33 (3H, s), 3.37 (2H, d, J=6.4 Hz), 4.03 (2H, d, J=6.5 Hz), 7.00 (2H, d, J=8.9 Hz), 7.4–7.6 (3H, m), 7.97 (2H, d, J=8.9 Hz), 8.12 (1H, d, J=8.2 Hz), 8.23 (2H, d, J=8.7 Hz), 8.39 (2H, d, J=8.7 Hz)

APCI-MASS: m/z=558 ($M+M^+$)

Preparation 238

1-[4-(4-n-Butoxyphenyl)cinnamoyl]benzotriazole 3-oxide

IR (KBr): 2952, 2867, 1778, 1598, 1496, 1249, 1186 cm^{-1}

NMR ($CDCl_3$, δ) 0.99 (3H, t, J=7.3 Hz), 1.55 (2H, tq, J=7.0 and 7.3 Hz), 1.78 (2H, tt, J=7.0 and 6.4 Hz), 4.02 (2H, t, J=6.4 Hz), 6.75 (1H, d, J=16.0 Hz), 7.00 (2H, d, J=8.7 Hz), 7.4–8.2 (9H, m)

APCI-MASS: m/z=414 ($M+M^+$)

Preparation 239

1-[4-[5-(4-Cyclohexylphenyl)-1,3,4-thiadiazol-2-yl] benzoyl]benzotriazole 3-oxide

IR (KBr): 2925, 2850, 1778, 1230, 999 cm^{-1}

NMR ($CDCl_3$, δ): 1.2–1.6 (5H, m), 1.7–2.0 (5m), 2.5–2.7 (1H, m), 7.37 (2H, d, J=8.3 Hz), 7.4–7.6 (3H, m), 7.97 (2H, d, J=8.3 Hz), 8.13 (1H, d, J=8.2 Hz), 8.26 (2H, d, J=8.6 Hz), 8.42 (2H, d, J=8.6 Hz)

APCI-MASS: m/z=482 $(M+H)^+$

Preparation 240

1-[4-[5-[4-(4-n-Propyloxyphenyl)phenyl]-1,3,4-oxadiazol-2-yl]benzoyl]benzotriazole 3-oxide

IR (KBr): 1778, 1604, 1488, 1249, 1232, 998 cm^{-1}

NMR ($CDCl_3$, δ) 1.07 (3H, t, J=7.4 Hz), 1.85 (2H, tq, J=6.5 and 7.4 Hz), 7.02 (2H, d, J=8.8 Hz), 7.4–7.7 (3H, m), 7.61 (2H, d, J=8.8 Hz), 7.75 (2H, d, J=8.5 Hz), 8.14 (1H, d, J=8.2 Hz), 8.22 (2H, d, J=8.5 Hz), 8.40 (2H, d, J=8.8 Hz), 8.48 (2H, d, J=8.8 Hz)

APCI-MASS: m/z=518 $(M+H)^+$

Preparation 241

1-[4-(5-n-Nonyl-1,3,4-oxadiazol-2-yl)benzoyl]-benzotriazole 3-oxide

IR (KBr): 2919, 2850, 1780, 1565, 1415, 1251 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.7 Hz), 1.2–1.6 (12H, m), 1.8–2.0 (2H, m), 2.98 (2H, t, J=7.7 Hz), 7.4–7.6 (3H, m), 8.12 (1H, d, J=9.0 Hz), 8.28 (2H, d, J=8.7 Hz), 8.42 (2H, d, J=8.7 Hz)

APCI-MASS: m/z=434 ($M+H^+$)

Preparation 242

1-[4-[3-(4-n-Hexyloxyphenyl)-1,2,4-oxadiazol-5-y]-benzoyl]benzotriazole 3-oxide

IR (KBr): 2946, 2869, 1780, 1251, 1230, 1001 cm^1

NMR ($CDCl_3$, δ) 0.92 (3H, t, J=6.8 Hz), 1.3–1.6 (6H, m), 1.8–1.9 (2H, m), 4.04 (2H, t, J=6.5 Hz), 7.03 (2H, d, J=8.9 Hz), 7.4–7.6 (3H, m), 8.0–8.2 (3H, 8.46 (4H, s)

APCI-MASS: m/z=484 ($M+M^+$)

Preparation 243

1-[4-[5-(4-n-Octyloxyphenyl)-1,3,4-thiadiazol-2-yl]-benzo-yl]benzotriazole 3-oxide

IR (KBr): 2925, 2856, 1774, 1602, 1259, 1232, 989 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=8.7 Hz), 1.1–1.6 (10H, m), 1.7–1.9 (2H, m), 4.04 (2H, t, J=6.5 Hz), 7.01 (2H, d, J=8.9 Hz), 7.4–7.6 (3H, m), 7.97 (2H, d, J=8.8 Hz), 8.12 (1H, d, J=8.2 Hz), 8.24 (2H, d, J=8.6 Hz), 8.40 (2H, d, J=8.6 Hz)

APCI-MASS: m/z=528 $(M+H^+)$

Preparation 244

1-[4-[5-(4-Trans-n-pentylcyclohexyl)-1,3,4-thiadiazol-2- yl]berzoyl]benzotriazole 3-oxide

IR (KBr): 2952, 2919, 2848, 1785, 1444, 1226, 991 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.9 Hz), (13H, m), 1.94 (2H, d, J=12.0 Hz), 2.27 (2H, d, J=12.0 Hz), 3.19 (1H, tt, J=12.0 and 3.6 Hz), 7.4–7.6 (3H, m), 8.12 (1H, d, J=8.0 Hz), 8.19 (2H, d, J=8.6 Hz), 8.38 (2H, d, J=8.6 Hz)

APCI-MASS: m/z=476 ($M+M^+$)

Preparation 245

1-[4-[3-(4-n-Pentyloxyphenyl)isoxazol-5-yl] benzoyl]benzotriazole 3-oxide

IR (KBr): 2948, 2867, 1776, 1610, 1436, 1253, 1002 cm^{-1}

NMR ($CDCl_3$, δ): 0.95 (3H, t, J=7.1 Hz), 1.2–1.6 (4H, m), 1.7–1.9 (2H, m), 4.02 (2H, t, J=6.5 Hz), 7.0–7.1 (3H, m), 7.4–7.6 (3H, m), 7.81 (2H, d, J=8.8 Hz), 8.06 (2H, d, J=8.6 Hz), 8.12 (1H, d, J=8.0 Hz), 8.39 (2H, d, J=8.6 Hz)

APCT-MASS: m/z=469 ($M+M^+$)

Preparation 246

1-[4-[5-[4-(8-Methoxyoctyloxy)phenyl]-1,3,4-oxadiazol-2-yl]benzoyl]benzotriazole 3-oxide

IR (KBr): 2923, 2854, 1787, 1608, 1494, 1255, 1228, 993 cm^{-1}

NMR ($CDCl_3$, δ): 1.2–1.6 (10H, m), 1.7–1.9 (2H, m), 3.34 (3H, s), 3.38 (2H, t, J=6.4 Hz), 4.05 (2H, t, J=6.5 Hz), 7.04 (2H, d, J=8.8 Hz), 7.4–7.6 (3H, s), 8.1–8.2 (3H, s), 8.36 (2H, d, J=8.7 Hz), 8.45 (2H, d, J=8.7 Hz)

APCI-MASS: m/z=542 ($M+M^+$)

Preparation 247

1-[4-[4-(6-Phenylpyridazin-3-yl-oxy]phenyl] benzoyl]-benzotriazole 3-oxide

IR (KBr): 1783, 1604, 1423, 1284, 985 cm^{-1}

NMR ($CDCl_3$, δ): 7.2–8.2 (15H, m), 8.12 (2H, d, J=8.3 Hz), 8.36 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=486 (M^++1)

Preparation 248

1-[4-[5-(4-n-Octyloxyphenyl)-1,3,4-oxadiazol-2-yl] benzoyl]benzotriazole 3-oxide

IR (KBr): 2925, 2854, 1780, 1610, 1496, 1257, 1228, 1180 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.8 Hz), 1.2–2.0 (12H, m), 4.05 (2H, t, J=6.5 Hz), 7.05 (2H, d, J=8.7 Hz) 7.4–7.6 (3H, m), 8.0–8.2 (3H, m), 8.37 (2H, d, J=8.6 Hz), 8.45 (2H, d, J=8.6 Hz)

APCI-MASS: m/z=512 ($M+H^+$)

Preparation 249

1-[4-[2-(4-n-Hexyloxyphenyl)pyrimidin-6-yl] benzoyl]-benzotriazole 3-oxide

IR (KBr): 2948, 2861, 1780, 1552, 1413, 1378, 987 cm^{-1}

NMR ($CDCl_3$, δ) 0.92 (3H, D J=6.8 Hz), 1.2–1.6(6H, m), 1.8–2.0 (2H, m), 4.06 (2H, t, J=6.5 Hz), 7.04 (2H, d, J=9.0 Hz), 7.4–7.6 (3H, m), 7.64 (1H, d, J=5.2 Hz), 8.13 (1H, d, J=8.2 Hz), 8.44 (4H, s), 8.55 (2H, d, J=9.0 Hz), 8.90 (1H, d, J=5.2 Hz)

APCI-MASS: m/z=494 ($M+M^+$)

Preparation 250

1-[4-[4-[8-(2-Ethoxyethoxy)octyloxy]phenyl] benzoyl]-benzotriazole 3-oxide

IR (KBr): 2933, 2861, 1778, 1598, 1247, 1186, 977 cm^{-1}

NMR ($CDCl_3$, δ): 1.22 (3H, t, J=7.0 Hz), 1.3–2.0 (14H, m), 3.4–3.6 (6H, m), 4.02 (2H, t, J=6.5 Hz), 7.02 (2H, d, J=8.8 Hz), 7.4–7.6 (3H, m), 7.62 (2H, d, J=8.8 Hz), 7.78 (2H, d, J=8.6 Hz), 8.10 (1H, d, J=8.9 Hz), 8.31 (2H, d, J=8.6 Hz)

APCI-MASS: m/z=532 ($M+M^+$)

Preparation 251

1-[4-[4-[7-(Piperidin-1-yl-carbonyl)heptyloxy] phenyl]-benzyl]benzotriazole 3-oxide

IR (KBr): 2935, 2856, 1774, 1631, 1598, 1255, 1191 cm^{-1}

NMR ($CDCl_3$, δ): 1.3–2.0 (16H, m), 2.37 (2H, t, J=7.6 Hz), 3.48 (4H, s), 4.02 (2H, t, J=6.4 Hz), 7.02 (2H, d, J=8.6 Hz), 7.4–7.6 (3H, m), 7.63 (2H, d, J=8.6 Hz), 7.78 (2H, d, J=8.3 Hz), 8.11 (1H, d, J=8.1 Hz), 8.31 (2H, d, J=8.3 Hz)

APCI-MASS: m/z=541 ($M+M^+$)

Preparation 252

1-[6-[4-(4-n-Heptyloxyphenyl)piperazin-1-yl] nicotinoyl]-benzotriazole 3-oxide

IR (KBr): 2929, 2856, 1762, 1604, 1510, 1240 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.7 Hz), 1.2–1.9 (10H, m), 3.20 (4H, t, J=5.0 Hz), 3.8–4.0 (6H, m), 6.75 (1H, d, J=9.5 Hz), 6.86 (2H, d, J=9.3 Hz), 6.95 (2H, d, J=9.3 Hz), 7.3–7.6 (3H, m), 8.10 (1H, d, J=8.2 Hz), 8.19 (1H, dd, J=9.2 and 2.3 Hz), 9.05 (1H, d, J=2.3 Hz)

APCI-MASS: m/z=515 ($M+M^+$)

Preparation 253

1-[6-[4-[4-(8-Methoxyoctyloxy)phenyl]piperazin-1-yl]nicotinoyl]benzotriazole 3-oxide

IR (KBr): 2929, 2854, 1766, 1602, 1510, 1419, 1234 cm^{-1}

NMR ($CDCl_3$, δ): 1.3–1.9 (12H, m), 3.2–3.3 (4H, m) 3.33 (3H, s), 3.36 (2H, t, J=6.4 Hz), 3.92 (2H, t, J=6.5 Hz), 4.0–4.2 (4H, m), 6.75 (1H, d, J=9.1 Hz), 6.87 (2H, d, J=8.9 Hz), 7.0–7.2 (2H, m), 7.4–7.6 (3H, m), 8.09 (1H, d, 8.1 Hz), 8.20 (1H, dd, J=9.1 and 2.3 Hz), 9.05 (1H, d, J=2.3 Hz)

APCI-MASS: m/z=559 ($M+H^+$)

Preparation 254

1-[4-[5-[4-(4-n-Propyloxyphenyl)phenyl]-1,3,4-thiadiazol-2-yl]benzoyl]benzotriazole 3-oxide

IR (KBr): 1774, 1600, 1234, 985 cm^{-1}

NMR ($CDCl_3$, δ): 1.07 (3H, t, J=7.3 Hz), 1.85 (2H, tq, J=6.5 and 7.3 Hz), 3.99 (2H, t, J=6.5 Hz), 7.01 (2H, d, J=8.7 Hz), 7.4–7.7 (5H, m), 7.72 (2H, d, J=8.7 Hz), 8.1–8.2 (2H, m), 8.28 (2H, d, J=8.6 Hz), 8.44 (2H, d, J=8.6 Hz)

APCI-MASS: m/z=534 $(M+H)^+$

The following compounds (Preparations 255 to 256) were obtained according to a similar manner to that of Preparation 32.

Preparation 255

6-Heptylnaphthalene-2-carboxylic acid

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.6 Hz), 1.15–1.53 (8H, m), 1.58–1.88 (2H, m), 2.80 (2H, t, J=7.6 Hz), 7.42 (1H, dd, J=1.7 and 8.4 Hz), 7.67 (1H, s), 7.84 (1H, d, J=8.6 Hz), 7.90 (1H, d, J=8.4 Hz), 8.09 (1H, dd, J=1.7 and 8.6 Hz), 8.68 (1H, s)

APCI-MASS: m/z=271 (M^++1), 285 (methyl $ester^+$–1)

Preparation 256

3-(E)-[4-[4-(7-Fluoroheptyloxy)phenyl]phenyl] acrylic acid

IR (KBr): 3037.3, 2935.1, 2861.8, 1679.7, 1633.4, 1600.6 cm^{-1}

NMR (DMSO-d_6, δ): 1.30–1.85 (10H, m), 4.01 (2H, t, J=6.4 Hz), 4.44 (2H, dt, J=47.6 and 6.1 Hz), 6.54 (1H, d, J=15.9 Hz), 7.02 (2H, d, J=8.7 Hz), 7.53–7.80 (7H, m)

Preparation 257

To a solution of 4-methylpentanol (3.0 ml) in pyridine (20 ml) were added in turn with p-toluenesulfonyl chloride (4.6 g) and 4-N,N-dimethylaminopyridine (1.5 g) at ambient temperature. After stirring at ambient temperature, the reaction mixture was taken up into a mixture of ethyl acetate (100 ml) and water (100 ml). The separated organic layer was washed in turn with hydrochloric acid (1N), water, aqueous sodium hydrogencarbonate, and brine, and dried over magnesium sulfate. Evaporation gave 1-p-Toluenesulfonyloxy-4-methylpentane (5.30g).

NMR ($CDCl_3$, δ): 0.83 (6H, d, J=6.6 Hz), 1.48 (1H, sept, J=6.6 Hz), 1.50–1.70 (2H, m), 2.45 (3H, s), 4.00 (2H, t, J=6.6 Hz), 7.34 (2H, d, J=8.1 Hz), 7.79 (2H, d, J=8.1 Hz)

APCI-MASS: m/z=257 (M^++1)

Preparation 258

To a solution of 4-bromo-4'-n-butyloxybiphenyl (3.05 g) in tetrahydrofuran (60 ml) was added 1.55 M n-butyllithium in n-hexane (7.74 ml) at −60° C. over a period of 10 minutes. The solution was stirred at −30° C. for 1.5 hours and cooled to −60° C. To the solution was added triisopropylborate (3.46 ml) over a period of 5 minutes, and the mixture was stirred for 1.5 hours without cooling. To the solution was added 1N hydrochloric acid (20 ml) and the solution was stirred for 30 minutes and extracted with ethyl acetate. The organic layer was separated and washed with water, brine and dried over magnesium sulfate. The solvents were removed under reduced pressure and the residue was triturated with n-hexane. The solid was collected by filtration and dried under reduced pressure to give 4-(4-n-Butyloxyphenyl)phenylboronic acid (2.31 g).

IR (KBr): 3398, 2956, 2919, 2871, 1604, 1531, 1392, 1257 cm^{-1}

NMR (DMSO-d_6, δ): 0.94 (3H, t, J=7.3 Hz), 1.4–1.8 (4H, m), 4.01 (2H, t, J=6.3 Hz), 7.01 (2H, d, J=8.7 Hz), 7.58 (2H, d, J=7.9 Hz), 7.62 (2H, d, J=8.7 Hz), 7.84 (2H, d, J=7.9 Hz), 8.03)2H, s)

The following compounds (Preparations 259 to 260) were obtained according to a similar manner to that of Preparation 258.

Preparation 259

4-[4-(6-Methoxyhexyloxy)phenyl]phenylboronic acid

IR (KBr): 3448, 3392, 2937, 2861, 1606, 1529, 1346, 1288 cm^{-1}

NMR (DMSO-d_6, δ): 1.3–1.8 (8H, m), 3.21 (3H, s), 3.31 (2H, t, J=6.3 Hz), 3.99 (2H, t, J=6.4 Hz), 7.00 (2H, d, J=8.7 Hz), 7.5–7.7 (4H, m), 7.84 (2H, d, J=8.1 Hz), 8.03 (2H, s)

APCI-MASS: m/z=329 ($M+H^+$)

Preparation 260

4-[4-(5-Methoxypentyloxy)phenyl]phenylboronic acid

IR (KBr): 3473, 3369, 3330, 2935, 2863, 1604, 1531, 1338, 1251 cm^{-1}

NMR (DMSO-d_6, δ): 1.4–1.8 (6H, m), 3.22 (3H, s), 3.3–3.4 (2H, m), 3.99 (2H, t, J=6.4 Hz), 7.00 (2H, d, J=8.7 Hz), 7.58 (2H, d, J=8.0 Hz), 7.61 (2H, d, J=8.7 Hz), 7.84 (2H, d, J=8.0 Hz), 8.04 (2H, s)

APCI-MASS: m/z=315 ($M+H^+$)

Preparation 261

To a suspension of 4-Methoxycarbonylphenyl boronic acid (648 mg) and 4-iodo-1-heptylpyrazole (876 mg) and $Pd(PPh_3)_4$ (173 mg) in 1,2-dimethoxyethane (10 ml) was added 2M Na_2CO_3 aq. (3.6 ml). The reaction mixture was stirred at 80° C. for 2 hours under N_2 atmosphere, and poured into ice-water and extracted with ethyl acetate. The organic layer was washed with brine, and dried over $MgSO_4$. The solvent was removed under pressure. The residue was subjected to column-chromatography on silica gel **60** (Merk) and eluted with n-hexane/ethyl acetate (80:20). The fractions containing the object compound were combined and evaporated under reduced pressure to give 1-heptyl-4-(4-methoxycarbonylphenyl)pyrazole (0.20 g).

IR (KBr pelet): 2952, 2920, 2848, 1712, 1610, 1288, 1114, 769 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.7 Hz), 1.1–1.4 (8H, m), 1.7–1.9 (2H, m), 3.85 (3H, s), 4.11 (2H, t, J=7.0 Hz), 7.72 (2H, d, J=8.5 Hz), 7.93 (2H, d, J=8.5 Hz), 7.99 (1H, s), 8.34 (1H, s)

APCI-MASS: m/z=301 ($M+H^+$)

The following compounds (Preparations 262 to 268) were obtained according to a similar manner to that of Preparation 261.

Preparation 262

Ethyl 4-[4-(4-n-butyloxyphenyl)phenyl]benzoate

IR (KBr): 2958, 2935, 2871, 1714, 1602, 1396, 1280, 1108 cm^{-1}

NMR ($CDCl_3$, δ): 0.99 (3H, t, J=7.3 Hz), 1.4–2.0 (7H, m), 4.02 (2H, t, J=6.4 Hz), 4.40 (2H, q, J=7.1 Hz), 6.98 (2H, d, J=6.8 Hz), 7.56 (2H, d, J=6.8 Hz), 7.66 (4H, s), 7.68 (2H, d, J=8.4 Hz), 8.12 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=375 $(M+H)^+$

Preparation 263

Methyl 6-(4-heptyloxyphenyl)nicotinate

IR (KBr): 2954, 2859, 1724, 1597, 1288, 1251, 1116, 783 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.6 Hz), 1.2–1.5 (8H, m), 1.7–1.9 (2H, m), 3.96 (3H, s), 4.03 (2H, t, J=6.5 Hz), 7.00 (2H, d, J=8.8 Hz), 7.75 (1H, d, J=8.4 Hz), 8.02 (1H, d, J=8.8 Hz), 8.30 (1H, dd, J=8.4 and 2.2 Hz), 9.23 (1H, d, J=2.2 Hz)

APCI-MASS: m/z=328 ($M+H^{30}$)

Preparation 264

Methyl 6-[4-(4-n-butyloxyphenyl)phenyl]nicotinate

IR (KBr): 2956, 2933, 2871, 1724, 1598, 1282, 1118 cm^{-1}

NMR ($CDCl_3$, δ): 1.00 (3H, t, J=7.3 Hz), 1.4–1.9 (4H, m), 3.98 (3H, s), 4.02 (2H, t, J=6.4 Hz), 7.00 (2H, d, J=8.8 Hz), 7.59 (2H, d, J=8.8 Hz), 7.70 (2H, d, J=8.5 Hz), 7.86 (1H, d, J=8.8 Hz), 8.13 (2H, d, J=8.5 Hz), 8.37 (1H, dd, J=8.8 and 1.6 Hz), 9.30 (1H, d, J=1.6 Hz)

APCI-MASS: m/z=362 ($M+H^{30}$)

Preparation 265

Methyl 5-[4-(4-n-butyloxyphenyl)phenyl]furan 2-carboxylate

IR (KBr): 2958, 2933, 2873, 1716, 1483, 1303, 1139 cm^{-1}

NMR ($CDCl_3$, δ): 0.99 (3H, t, J=7.3 Hz), 1.5–1.9 (4H, m), 3.93 (3H, s), 4.01 (2H, t, J=6.4 Hz), 6.75 (1H, d, J=3.6 Hz), 6.98 (2H, d, J=8.7 Hz), 7.26 (1H, d, J=3.6 Hz), 7.56 (2H, d, J=8.4 Hz), 7.61 (2H, d, J=8.7 Hz), 7.83 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=351 $(M+H)^+$

Preparation 266

Ethyl 4-[4-[4-(6-methoxyhexyloxy)phenyl]phenyl] benzoate

IR (KBr): 2937, 2863, 1712, 1602, 1396, 1278, 1108 cm^{-1}

NMR ($CDCl_3$, δ): 1.4–2.0 (11H, m), 3.34 (3H, s), 3.39 (2H, t, J=6.4 Hz), 4.01 (2H, t, J=6.4 Hz), 4.41 (2H, q, J=7.1 Hz), 6.98 (2H, d J=8.7 Hz), 7.56 (2H, d, J=8.7 Hz), 7.6–7.8 (6H, m), 8.12 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=433 $(M+H^+)$

Preparation 267

4-[4-[4-(5-Methoxypentyloxy)phenyl]phenyl] benzoic acid

IR (KBr): 2939, 2859, 1679, 1587, 1396, 1321, 1292, 1126 cm^{-1}

NMR (DMSO-d_6, δ): 1.3–1.8 (6H, m), 3.21 (3H, s), 3.2–3.4 (2H, m), 4.01 (2H, t, J=6.5 Hz), 7.04 (2H, d, J=8.6 Hz), 7.66 (2H, d, J=8.6 Hz), 7.7–7.9 (6H, m), 8.03 (2H, d, J=8.2 Hz)

APCI-MASS: m/z=391 $(M+H^+)$

Preparation 268

Methyl 4-[4-[4-(5-methoxypentyloxy)phenyl] phenyl]phenyl acetate

IR (KBr): 2937, 2863, 1739, 1604, 1492, 1255 cm^{-1}

NMR ($CDCl_3$, δ): 1.5–2.0 (6H, m), 3.34 (3H, s), 3.42 (2H, t, J=6.3 Hz), 3.68 (2H, s), 3.72 (3H, s), 4.02 (2H, t, J=6.4 Hz), 6.97 (2H, d, J=8.7 Hz), 7.36 (2H, d, J=8.2 Hz), 7.5–7.7 (8H, m)

APCI-MASS: m/z=419 $(M+H^+)$

Preparation 269

A solution of 3-[2-(4-Hexylphenylamino)ethyl]-2-oxo-oxazolidine hydrochloride (2.131 g) in 25% hydrobromic acid in acetic acid (13.04 ml) was stirred for 96 hours at ambient temperature. The reaction mixture was pulverized with diisopropyl ether. The precipitate was collected by filtration and added to ethanol (15 ml). The solution was refluxed for 5 hours and pulverized with diisopropyl ether. The precipitate was collected by filtration to give 1-(4-n-Hexylphenyl)piperazine dihydrobromide (2.413 g).

IR (KBr): 2921.6, 2711.4, 2485.8, 1452.1, 1012.4 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.6 Hz), 1.1–1.4 (6H, m), 1.4–1.6 (2H, m), 2.49 (2H, t, J=8.4 Hz), 3.1–3.4 (8H, m), 6.54 (2H, s), 6.90 (2H, d, J=8.7 Hz), 7.08 (2H, d, J=8.7 Hz), 8.78 (1H, s)

APCI-MASS: m/z=247 $(M^+ + H)$

The following compounds (Preparations 270 to 274) were obtained according to a similar manner to that of Preparation 269.

Preparation 270

4-[4-(4-n-Hexylphenyl)piperazin-1-yl]benzoic acid dihydrobromide

IR (KBr): 2956.3, 1691.3, 1664.3, 1602.6, 1232.3 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.5 Hz), 1.2–1.4 (10H, m), 1.4–1.6 (2H, m), 2.51 (2H, t, J=7.4 Hz), 3.2–3.6 (8H, m), 7.0–7.2 (6H, m), 7.81 (2H, d, J=8.8 Hz)

APCI-MASS: m/z=367 $(M^+ + H)$

Preparation 271

1-(4-Cyclohexylphenyl)piperazine dihydrobromide

IR (KBr): 2927.4, 1510.0, 1452.1 cm^{-1}

NMR (DMSO-d_6- δ): 1.1–1.5 (6H, m), 1.6–1.9 (4H, m), 2.41 (1H, m), 3.1–3.4 (8H, m), 6.91 (2H, d, J=8.7 Hz), 7.11 (2H, d, J=8.7 Hz), 8.78 (1H, s)

APCI-MASS: m/z=245 $(M^+ + H)$

Preparation 272

4-[4-(4-Cyclohexylphenyl)piperazin-1-yl]benzoic acid dihydrobromide

IR (KBr): 1668.1, 1602.6, 1230.4, 1189.9 cm^{-1}

APCI-MASS: m/z=365 $(M^+ + H)$

Preparation 273

3-Fluoro-4-[4-(4-hydroxyphenyl)piperazin-1-yl] benzoic acid dihydrobromide

IR (KBr): 1708.6, 1610.3 cm^{-1}

NMR (DMSO-d_6, δ): 3.2–3.6 (8H, m), 6.81 (2H, d, J=8.6 Hz), 7.0–7.4 (3H, m), 7.4–7.8 (2H, m)

APCI-MASS: m/z=317 $(M^+ + H)$

Preparation 274

4-[4-(4-Hydroxyphenyl)piperazin-1-yl]benzoic acid dihydrobromide

IR (KBr): 1670.1, 1604.5, 1226.5, 775.2 cm^{-1}

NMR (DMSO-d_6, δ): 3.0–3.2 (4H, m), 3.3–3.5 (4H, m), 6.68 (2H, d, J=8.8 Hz), 6.85 (2H, d, J=8.8 Hz), 7.02 (2H, d, J=8.8 Hz), 6.85 (2H, d, J=8.8 Hz, 8.86 (1H, s), 12.29 (1H, s)

APCI-MASS: m/z=299 $(M+H^+)$

Preparation 275

A mixture of 4-n-hexyloxyaniline (10 g), ethyl acrylate (56.1 ml), glacial acetic acid (19.25 ml), and cuprous chloride (1.02 g) was heated under reflux with stirring under nitrogen for 26 hours. A solution of the cold product in ether was shaken with water and then with aqueous ammonia. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and filtrate was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel and eluted with hexane-ethyl acetate (9:1). The fractions containing the object compound were combined and evaporated under reduced pressure to give Ethyl 3-[N-(2-ethoxycarbonylethyl)-N-(4-hexyloxyphenyl)amino] propionate (15.756 g).

IR (Neat): 1733.7, 1513.8, 1241.9, 1182.2 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.5 Hz), 1.2–1.55 (6H, m), 1.24 (6H, t, J=7.1 Hz), 1.65–1.85 (2H, m), 2.51 (4H, t,

J=7.2 Hz), 3.53 (4H, t, J=7.2 Hz), 3.89 (2H, t, J=6.5 Hz), 4.12 (4H, q, J=7.1 Hz), 6.72 (2H, d, J=9.3 Hz), 6.83 (2H, d, J=9.3 Hz)

APCI-MASS: m/z=394 (M^++H)

Preparation 276

A suspension of methyl 4-formylbenzoate (4.92 g), hydroxylamine hydrochloride (5.21 g) and sodium acetate (6.15 g) in ethanol (50 ml) was refluxed for 2 hours. The mixture was poured into water and extracted with ethyl acetate and the separated organic layer was washed with brine and dried over magnesium sulfate. The solvents were removed under reduced pressure to give 4-methoxycarbonyl-benzaldehyde oxime (5.28 g).

IR (KBr): 3291, 1727, 1438, 1284, 1112 cm^{-1}

NMR ($CDCl_3$, δ): 3.93 (3H, s), 7.65 (2H, d, J=8.3 Hz), 8.10 (2H, d, J=8.3 Hz), 8.18 (1H, s), 8.27 (1H, s)

APCI-MASS: m/z=180

The following compound was obtained according to a similar manner to that of Preparation 276.

Preparation 277

N-Hydroxy-4-n-hexyloxybenzamidine

IR (KBr): 3446, 3349, 2937, 2865, 1650, 1610, 1519, 1392, 1253 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.4 Hz), 1.2–1.8 (8H, m), 3.97 (2H, t, J=6.5 Hz), 5.70 (2H, s), 6.90 (2H, d, J=8.4 Hz), 7.58 (2H, d, J=8.4 Hz), 9.43 (1H, s)

APCI-MASS: m/z=237 $(M+H)^+$

Preparation 278

To a solution of 4-methoxycarbonylbenzaldehyde oxime (896 mg) in N,N-dimethylformamide (10 ml) was added 4N-hydrochloride acid in 1,4-dioxane (1.38 ml) and oxone® (1.69 g). The suspension was stirred at ambient temperature for 16 hours and poured into ice-water. The object compound was extracted with ethyl acetate and the organic layer was washed with brine, dried over magnesium sulfate. The solvents were removed under reduced pressure to give 4-Methoxycarbonylbenzaldehyde oxime chloride (1.05 g).

IR (KBr): 3390, 1710, 1436, 1405, 1284, 1232, 1116, 1016 cm^{-1}

NMR ($CDCl_3$, δ): 3.95 (3H, s), 8.93 (2H, d, J=8.3 Hz), 8.10 (2H, d, J=8.7 Hz), 8.39 (1H, s)

APCI-MASS: m/z=176 ($M-H^+$–HCl)

Preparation 279

A solution of Ethyl 4-oxo-1-(4-n-hexyloxyphenyl) piperidine-3-carboxylate (1.437 g) in 20% hydrochloric acid (7.2 ml) was refluxed for 2 hours, cooled, basified with 60% aqueous sodium hydroxide, and extracted with ethyl acetate. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and filtrate was evaporated under reduced pressure to give 1-(4-n-Hexyloxyphenyl)-4-piperidone (0.959 g).

IR (Neat): 2931.3, 1716.3, 1511.9, 1243.9, 825.4 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.5 Hz), 1.2–1.6 (6H, m), 1.65–1.85 (2H, m), 2.57 (4H, t, J=6.1 Hz), 3.46 (4H, t, J=6.1 Hz), 3.92 (2H, t, J=6.5 Hz), 6.85 (2H, d, J=9.3 Hz), 6.95 (2H, d, J=9.3 Hz)

APCI-MASS: m/z=276 (M^++H)

Preparation 280

A solution of 4-[4-(7-Bromoheptyloxy)phenyl] bromobenzene (0.25 g) in a solution of tetra n-butylammonium fluoride (tetrahydrofuran solution, 1M, 2.9 ml) was heated to 50° C. for 2 hours. After cooling to ambient temperature, the solution was taken up into a mixture of ethyl acetate (20 ml) and water (20 ml). The separated organic layer was washed with water, brine, and dried over magnesium sulfate. Evaporation gave a residue which was chromatographed on silica gel (30 ml) eluting with a mixture of n-hexane and ethyl acetate (100:0–97:3, V/V). The fractions which contained the objective compound were collected and evaporated a residue which was triturated with n-hexane to give 4-[4-(7-Fluoroheptyloxy) phenyl]bromobenzene (104 mg).

IR (KBr): 2937.1, 2859.9, 1606.4 cm^{-1}

NMR ($CDCl_3$, δ): 1.20–1.90 (10H, m), 3.99 (2H, t, J=6.4 Hz), 4.45 (2H, dt, J=47.3 and 6.1 Hz), 6.95 (2H, d, J=6.7 Hz), 7.40 (2H, d, J=6.7 Hz), 7.47 (2H, d, J=6.7 Hz), 7.52 (2H, d, J=6.7 Hz)

The following compound was obtained according to a similar manner to that of Preparation 280.

Preparation 281

4-[4-(6-Fluorohexyloxy)phenyl]bromobenzene

NMR ($CDCl_3$, δ): 1.40–1.95 (8H, m), 4.01 (2H, t, J=6.4 Hz), 4.47 (2H, dt, J=47.5 and 6.0 Hz), 6.95 (2H, d, J=8.6 Hz), 7.35–7.59 (6H, m)

Preparation 282

A solution of 4-[4-(8-Bromooctyloxy)phenyl] bromobenzene (3.7 g) in a mixture of sodium methoxide (4.9M in methanol, 17 ml), N,N-dimethylformamide (20 ml) and tetrahydrofuran (8 ml) was heated to 80° C. for 3 hours. The reaction mixture was taken up into a mixture of ethyl acetate (200 ml) and water (100 ml). The separated organic layer was washed in turn with water, brine, dried over magnesium sulfate. Evaporation gave a residue which was subjected to column chromatography (silica gel, 100 ml) eluting with n-hexane to give 4-[4-(8-Methoxyoctyloxy) phenyl]bromobenzene (2.73 g).

IR (KBr): 2935.1, 2858.0, 1604.5 cm^{-1}

NMR ($CDCl_3$, δ): 1.25–1.70 (10H, m), 1.70–1.95 (2H, m), 3.33 (3H, s), 3.37 (2H, t, J=6.5 Hz), 3.99 (2H, t, J=6.5 Hz), 6.95 (2H, d, J=8.8 Hz), 7.35–7.66 (6H, m)

APCI-MASS: m/z=391 (M^+)

The following compounds (Preparation 283 to 284) were obtained according to a similar manner to that of Preparation 282.

Preparation 283

4-[4-(6-Methoxyhexyloxy)Phenyl]Bromobenzene

NMR ($CDCl_3$, δ): 1.50–1.70 (6H, m), 1.70–1.95 (2H, m), 3.34 (3H, s), 3.40 (2H, t, J=6.2 Hz), 3.99 (2H, t, J=6.5 Hz), 6.95 (2H, d, J=8.7 Hz), 7.30–7.60 (6H, m)

APCI-MASS: m/z=365 (M^++2)

Preparation 284

4-[4-(7-Methoxyheptyloxy)Phenyl]Bromobenzene

IR (KBr): 2935.1, 2854.1, 1604.5 cm^{-1}

NMR ($CDCl_3$, δ): 1.25–1.70 (8H, m), 1.70–1.95 (2H, m), 3.33 (3H, s), 3.37 (2H, t, J=6.4 Hz), 3.98 (2H, t, J=6.5 Hz), 6.95 (2H, d, J=8.8 Hz), 7.35–7.56 (6H, m)

APCI-MASS: m/z=379 (M^++2)

Preparation 285

N-(4-octylphenyl)-N'-aminourea, Formamidine acetate (12.76 g) and N-carbazoyl-4-octylaniline (6.458 g) in N,N-dimethylformamide (19.4 ml) were stirred at 150° C. for 6 hours. The reaction mixture was pulverized with water. The precipitate was collected by filtration and washed with water to give 4-(4-Octylphenyl)-2,3-dihydro-4H-1,2,4-triazol-3-one (4.27 g).

IR (KBr): 3214.8, 3085.5, 1704.8 cm^{-1}

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.7 Hz), 1.2–1.5 (10H, m), 1.5–1.8 (2H, m), 2.64 (2H, t, J=7.9 Hz), 7.29 (2H, d, J=8.5 Hz), 7.43 (2H, d, J=8.5 Hz), 7.67 (1H, d, J=1.3 Hz), 10.31 (1H, s)

APCI-MASS: m/z=274 ($M+H^+$)

The following compound (Preparation 286) was obtained according to a similar manner to that of Preparation 285.

Preparation 286

4-[4-(4-Tert-Butoxycarbonylpiperazin-1-yl)Phenyl]-2,3-Dihydro-4H-1,2,4-Triazol-3-One

IR (KBr): 3200, 1699.0, 918.0 cm^{-1}

NMR ($CDCl_3$, δ): 1.49 (9H, s), 3.17 (4H, t, J=4.9 Hz), 3.60 (4H, t, J=4.9 Hz), 7.00 (2H, d, J=9.0 Hz), 7.40 (2H, d, J=9.0 Hz), 7.63 (1H, s), 10.4 (1H, s)

APCI-MASS: m/z=346 ($M+H^+$)

Preparation 287

A mixture of Methyl 6-(1-heptynyl)naphthalene-2-carboxylate (4.51 g) and platinum oxide (0.4 g) in tetrahydrofuran was stirred under 3.5 atm pressure of hydrogen for 5 hours. The catalyst was filtered off and the filtlate was evaporated to give Methyl 6-heptylnaphthalene-2-carboxylate (4.40 g).

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.6 Hz), 1.16–1.50 (8H, m), 1.50–1.80 (2H, m), 2.78 (2H, t, J=7.6 Hz), 3.97 (3H, s), 7.39 (1H, dd, J=17 and 8.4 Hz), 7.64 (1H, s), 7.79 (1H, d, J=8.6 Hz), 7.86 (1H, d, J=8.4 Hz), 8.02 (1H, dd, J=1.7 and 8.6 Hz), 8.57 (1H, s)

APCI-MASS: m/z=285 (M^++1)

The following compound (Preparation 288) was obtained according to a similar manner to that of Preparation 287.

Preparation 288

Methyl 6-Hexylnaphthalene-2-Carboxylate

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.8 Hz), 1.17–1.53 (6H, m), 1.60–1.82 (2H, m), 2.79 (2H, t, J=7.7 Hz), 3.97 (3H, s),, 7.39 (1H, dd, J=1.7 and 8.4 Hz), 7.64 (1H, s), 7.80 (1H, d, J=8.6 Hz), 7.86 (1H, d, J=8.4 Hz), 8.03 (1H, dd, J=1.7 and 8.6 Hz), 8.57 (1H, s)

APCI-MASS: m/z=271 (M+1)

Preparation 289

To a stirred solution of Methyl 6-hydroxynaphthalene-2-carboxylate (3.0 g) in dichloromethane (40 ml) were added in turn diisopropylethylamine (3.9 ml) and triflic anhydride (3.0 ml) at −40° C. After stirring at −40° C. for 20 minutes, the mixture was taken up into a mixture of ethyl acetate and cold water. The organic layer was separated, washed with brine, dried over magnesium sulfate, and dried in vacuo. The residue was taken up into piperidine (20 ml) and to the solution were added 1-heptyne (4.0 ml) and tetrakis (triphenylphosphine)palladium(0) (0.5 g). After heating to 85° C. for 1 hour under nitrogen atmosphere, the reaction mixture was evaporated in vacuo. The residue was diluted with ethyl acetate, and the solution was washed in turn with hydrochloric acid and brine, dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (9:1, V/V) to give Methyl 6-(1-heptynyl) naphthalene-2-carboxylate (4.01 g).

NMR ($CDCl_3$, δ): 0.94 (3H, t, J=7.2 Hz), 1.30–1.70 (6H, m), 2.46 (2H, t, J=7.0 Hz), 3.97 (3H, s), 7.50 (1H, dd, J=1.7 and 8.6 Hz), 7.80 (1H, d, J=8.6 Hz), 7.86 (1H, d, J=8.6 Hz), 8.04 (1H, dd, J=1.7 and 8.6 Hz), 8.55 (1H, s)

APCI-MASS: m/z=281 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 289.

Preparation 290

Methyl 6-(1-Hexynyl)Naphthalene-2-Carboxylate

NMR ($CDCl_3$, δ): 0.97 (3H, t, J=7.1 Hz), 1.40–1.71 (4H, m), 2.47 (2H, t, J=6.8 Hz), 3.98 (3H, s), 7.50 (1H, dd, J=1.5 and 8.5 Hz), 7.79 (1H, d, J=8.6 Hz), 7.85 (1H, d, J=8.5 Hz), 7.92 (1H, s), 8.04 (1H, dd, J=1.7 and 8.6 Hz), 8.55 (1H, s)

APCI-MASS: m/z=267 (M^++1)

Preparation 291

To a solution of 4-octylaniline (5 ml) in a mixture of pyridine (12.5 ml) and chloroform (40 ml) was added phenyl chloroformate (2.95 ml) and stirred for 1.5 hours at ambient temperature. The reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 4-Octyl-N-phenoxycarbonylaniline (4.51 g)

IR (KBr): 3318.9, 1714.4, 1234.2 cm^{-1}

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.2 Hz), 1.2–1.4 (10H, m), 1.5–1.7 (2H, m), 2.57 (2H, t, J=7.3 Hz), 6.88 (1H, s), 7.1–7.5 (9H, m)

The following compounds (Preparations 292 to 299) were obtained according to a similar manner to that of Preparation 291.

Preparation 292

4-(4-Tert-Butoxycarbonylpiperazin-1-yl)-N-Phenoxycarbonylaniline

IR (KBr): 3309.2, 1743.3, 1658.5, 1197.6 cm^{-1}

NMR ($CDCl_3$, δ): 1.48 (9H, s), 3.08 (4H, t, J=5.3 Hz), 3.58 (4H, t, J=5.3 Hz), 6.87 (1H, s), 6.91 (2H, d, J=9 Hz), 7.1–7.5 (7H, m)

APCI-MASS: m/z=398 ($M+H^+$)

Preparation 293

1-(4-Cyclohexylbenzoyl)-2-(4-Methoxycarbonylbenzoyl)Hydrazine

IR (KBr): 3236, 2925, 2852, 1726, 1679, 1637, 1278, 1110 cm^{-1}

NMR (DMSO-d_6, δ): 1.1–1.5 (5H, m), 1.6–2.0 (5H, m), 2.60 (1H, m), 3.90 (3H, s), 7.37 (2H, d, J=8.0 Hz), 7.85 (2H, d, J=8.0 Hz), 8.0–8.2 (4H, m), 10.48 (1H, s), 10.68 (1H, s)

APCI-MASS: m/z=381 $(M+H)^+$

Preparation 294

1-[4-(Piperidin-1-yl)Benzoyl]-2-(4-Methoxycarbonylbenzoyl]Hydrazine

IR (KBr): 3500, 3286, 2941, 2854, 1712, 1689, 1650, 1606, 1286, 1242 cm^{-1}

NMR (DMSO-d_6, δ): 1.59 (6H, s), 3.33 (4H, s), 3.90 (3H, s), 6.97 (2H, d, J=8.8 Hz), 7.79 (2H, d, J=8.8 Hz), 8.02 (2H, d, J=8.4 Hz), 8.09 (2H, d, J=8.4 Hz), 10.23 (1H, s), 10.57 (1H, s)

APCI-MASS: m/z=382 $(M+H)^+$

Preparation 295

1-[4-(4-n-Propyloxyphenyl)Benzoyl]-2-(4-Methoxycarbonylbenzoyl]Hydrazine

IR (KBr): 3230, 1724, 1679, 1654, 1280, 1108 cm^{-1}

NMR (DMSO-d_6, δ): 1.00 3H, d, J=7.5 Hz), 1.76 (2H, tq, J=6.5 and 7.5 Hz), 3.91 (3H, s), 7.05 (2H, d, J=8.7 Hz), 7.71 (2H, d, J=8.7 Hz), 7.79 (2H, d, J=8.5 Hz), 8.00 (2H, d, J=8.5 Hz), 8.05 (2H, d, J=8.6 Hz), 8.11 (2H, d, J=8.6 Hz), 10.60 (1H, s), 10.72 (1H, s)

APCI-MASS: m/z=433 $(M+H)^+$

Preparation 296

1-(4-Methoxycarbonylbenzoyl)-2-Decanoylhydrazine

IR (KBr): 3320, 2919, 2850, 1724, 1643, 1600, 1567, 1479, 1284 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.8 Hz), 1.2–1.7 (14H, m), 2.18 (2H, t, J=7.4 Hz), 3.89 (3H, s), 7.97 (2H, d, J=8.5 Hz), 8.06 (2H, d, J=8.5 Hz), 9.15 (1H, s), 10.49 (1H, s)

APCI-MASS: m/z=349 $(M+H^+)$

Preparation 297

1-(4-Methoxycarbonylbenzoyl)-2-(Trans-4-n-Pentylcyclohexylcarbonyl)Hydrazine

IR (KBr): 3201, 2923, 2852, 1727, 1600, 1567, 1479, 1282 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.9 Hz), 0.9–1.0 (2H, m), 1.1–1.5 (11H, m), 1.7–1.9 (4H, m), 2.20 (1H, m), 3.88 (3H, s), 7.97 (2H, d, J=8.6 Hz), 8.06 (2H, d, J=8.6 Hz), 9.85 (1H, s), 10.46 (1H, s)

APCI-MASS: m/z=375 $(M+H^+)$

Preparation 298

1-[4-(8-Methoxyoctyloxy)Benzoyl]-2-(4-Methoxycarbonylbenzoyl)Hydrazine

IR (KBr): 3213, 2935, 2856, 1718, 1600, 1567, 1465, 1282 cm^{-1}

NMR (DMSO-d_6, δ): 1.2–1.8 (12H, m), 3.21 (3H, s), 3.29 (2H, t, J=6.4 Hz), 3.90 (3H, s), 4.04 (2H, t, J=6.5 Hz), 7.04 (2H, d, J=8.8 Hz), 7.90 (2H, d, J=8.8 Hz), 8.04 (2H, d, J=8.7 Hz), 8.10 (2H, d, J=8.7 Hz), 10.41 (1H, s), 10.64 (1H, s)

APCI-MASS: m/z=457 $(M+H^+)$

Preparation 299

1-(4-Octyloxybenzoyl)-2-(4-Methoxycarbonylbenzoyl)Hydrazine

IR (KBr): 3224, 2923, 2854, 1724, 1681, 1643, 1502, 1434, 1282, 1253, 1106 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.8 Hz), 1.2–1.5 (10H, m), 1.6–1.8 (2H, m), 3.89 (3H, s), 4.04 (2H, t, J=6.3 Hz), 7.04 (2H, d, J=8.7 Hz), 7.90 (2H, d, J=8.7 Hz), 8.03 (2H, d, J=8.6 Hz), 8.10 (2H, d, J=8.6 Hz), 10.42 (1H, s), 10.64 (1H, s)

APCI-MASS: m/z=427 $(M+H^+)$

Preparation 300

A solution of Methyl 4-n-hexyloxybenzoate (2.00 g) and hydrazine hydrate (4.24 g) in ethanol (10 ml) was refluxed for 6 hours. After cooling, the reaction mixture was poured into water. The precipitate was collected by filtration, washed with water and dried over P_2O_5 under reduced pressure to give N-(4-n-hexyloxybenzoyl)hydrazine (1.96 g).

IR (KBr): 3311, 2954, 2869, 1623, 1253 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.8 Hz), 1.2–1.5 (6H, m), 1.6–1.8 (2H, m), 4.00 (2H, t, J=6.5 Hz), 4.40 (2H, s), 6.95 (2H, d, J=8.6 Hz), 7.77 (2H, d, J=8.6 Hz), 9.59 (1H, s)

APCI-MASS: m/z=237 $(M+H)^+$

The following compounds (Preparations 301 to 308) were obtained according to a similar manner to that of Preparation 300.

Preparation 301

N-(4-Octylphenyl)-N'-Aminourea

IR (KBr): 3309.2, 1683.6, 1554.3 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.7 Hz), 1.1–1.4 (10H, m), 1.4–1.6 (2H, m), 2.48 (2H, t, J=8.9 Hz), 4.32 (2H, s), 7.03 (2H, d, J=8.4 Hz), 7.32 (1H, s), 7.38 (2H, d, J=8.4 Hz), 8.50 (1H, s)

Preparation 302

N-[4-(4-Tert-Butoxycarbonylpiperazin-1-yl)Phenyl]-N'-Aminourea

IR (KBr): 3237.9, 1695.1, 1670.1, 1540.8, 1230.4 cm^{-1}

NMR (DMSO-d_6, δ): 1.42 (9H, s), 2.97 (4H, t, J=4.9 Hz), 3.44 (4H, t, J=4.9 Hz), 4.30 (2H, s), 6.85 (2H, d, J=9.0 Hz), 7.26 (1H, s), 7.36 (2H, d, J=9.0 Hz), 8.41 (1H, s)

Preparation 303

4-Cyclohexylbenzoylhydrazine

IR (KBr): 3318, 2925, 2852, 1625, 1606, 1527, 1326 cm^{-1}

NMR (DMSO-d_6, δ): 1.1–1.5 (5H, m), 1.6–2.0 (5H, m), 2.4–2.6 (1H, m), 4.44 (2H, s), 7.27 (2H, d, J=8.2 Hz), 7.73 (2H, d, J=8.2 Hz), 9.66 (1H, s)

APCI-MASS: m/z=219 $(M+H)^+$

Preparation 304

4-(Piperidin-1-yl)Benzoylhydrazine

IR (KBr): 3263, 2852, 1612, 1504, 1245, 1124 cm^{-1}

NMR (DMSO-d_6, δ): 1.57 (6H, s), 3.25 (4H, s), 4.35 (2H, s), 6.90 (2H, d, J=9.0 Hz), 7.68 (2H, d, J=9.0 Hz), 9.44 (1H, s)

APCI-MASS: m/z=220 $(M+H)^+$

Preparation 305

4-(4-n-Propyloxyphenyl)Benzoylhydrazine

IR (KBr): 3350, 3276, 1610, 1494, 1288, 978 cm^{-1}

NMR (DMSO-d_3, δ): 0.99 (3H, t, J=7.5 Hz), 1.75 (2H, tq, J=6.5 and 7.5 Hz), 3.98 (2H, t, J=6.5 Hz), 4.50 (2H, s), 7.03

(2H, d, J=8.8 Hz), 7.65 (2H, d, J=8.8 Hz), 7.69 (2H, d, J=8.4 Hz), 7.88 (2H, d, J=8.4 Hz), 9.79 (1H, s)

APCI-MASS: m/z=271 ($M+H^+$)

Preparation 306

4-Methoxycarbonylbenzoylhydrazine

IR (KBr): 3322, 3250, 3018, 1727, 1658, 1621, 1565, 1432, 1280, 1110 cm^{-1}

NMR (DMSO-d_6, δ): 3.87 (3H, s), 4.58 (2H, s), 7.93 (2H, dd, J=8.6 and 3.1 Hz), 7.02 (2H, dd, J=8.6 and 3.1 Hz), 9.97 (1H, s)

APCI-MASS: m/z=195 ($M+H^+$)

Preparation 307

Trans-4-n-Pentylcyclohexylcarbonylhydrazine

IR (KBr): 3303, 3199, 2954, 2925, 2850, 1639, 1619, 1533, 1457 cm^{-1}

NMR (DMSO-d_6, δ): 0.8–1.0 (6H, m), 1.1–1.5 (10H, m), 1.6–2.2 (5H, m), 4.10 (2H, s), 8.85 (1H, s)

APCI-MASS: m/z=213 ($M+H^+$)

Preparation 308

4-(8-Methoxyoctyloxy)Benzoylhydrazine

IR (KBr): 3309, 2937, 2852, 1606, 1494, 1253 cm^{-1}

NMR (DMSO-d_6, δ): 1.2–1.8 (12H, m), 3.20 (3H, s), 3.25 (2H, t, J=6.5 Hz), 3.99 (2H, t, J=6.5 Hz), 4.39 (2H, s), 6.95 (2H, d, J=8/8 Hz), 7.77 (2H, d, J=8/8 Hz), 9.58 (1H, s)

APCI-MASS: m/z=295 $(M+H)^+$

Preparation 309

To a stirred solution of 4-bromo-4'-n-heptylbiphenyl (2.71 g) in tetrahydrofuran (100 ml) was added dropwise a solution of n-butyllithium in a mixture of diethyl ether and n-hexane (1.6M, 5.1 ml) at −78° C. After stirring at −78° C. for 30 minutes, the resultant mixture was added to a solution of diethyl oxalate (3.4 ml) in tetrahydrofuran (50 ml) at −78° C. The resultant mixture was allowed to warm to 0° C. for about 1 hour, and to the mixture was added acetic acid (0.5 ml). Evaporation gave a residue which was taken up into a mixture of water and ethyl acetate. The organic layer was separated, washed with brine, dried over magnesium sulfate. Evaporation gave a residue which was chromatographed on silica gel (200 ml) eluting with a mixture of n-hexane and ethyl acetate (10:0–95:5, V/V) to give 1-Ethyl-2-(4-n heptylphenyl)ethanedione (2.23 g).

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.6 Hz), 1.10–1.50 (8H, m), 1.44 (3H, t, J=7.1 Hz), 1.50–1.80 (2H, m), 2.66 (2H, t, J=7.7 Hz), 4.47 (2H, q, J=7.1 Hz), 7.20–7.40 (2H, m), 7.50–7.64 (2H, m), 7.64–7.85 (2H, m), 8.00–8.20 (2H, m)

APCI-MASS: m/z=353 (M^++1)

Preparation 310

To a suspension of sodium hydride (60% in oil, 0.37 g) in tetrahydrofuran (40 ml) was added by portions 4-acetyl-4'-n-heptylbiphenyl (2.50 g) at ambient temperature. After stirring at ambient temperature for 1 hours, to the solution was added triethyl phosphonoacetate (1.9 ml) and the mixture was heated to reflux for 5 hours. After cooling to ambient temperature, to the mixture was added acetic acid (0.53 ml) and evaporated. The residue was taken up into a mixture of water and ethyl acetate. The separated organic layer was washed with brine, dried over magnesium sulfate and evaporated. The residue was chromatographed on silica gel (200 ml) eluting with mixture of n-hexane and diisopropyl ether (99:1–20:1, V/V) to give Ethyl (E)-3-[4-(4-heptylphenyl)phenyl]-2-butenoate (2.19 g).

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.6 Hz), 1.13–1.48 (8H, m), 1.48–1.78 (2H, m), 2.61 (3H, s), 2.65 (2H, t, J=7.4 Hz), 4.22 (2H, q, J=7.1 Hz), 6.20 (1H, t, J=2.7 Hz), 7.23–7.28 (2H, m), 7.50–7.63 (6H, m)

APCI-MASS: m/z=365 (M^++1)

Preparation 311

To a solution of 4-bromo-4'-n-heptylbiphenyl (5.1 g) in tetrahydrofuran (60 ml) was added a solution of #n-butyllithium in a mixture of n-hexane and diethyl ether (1.6M, 9.7 ml) at −60° C. After stirring at −60° C. for 30 minutes, to the mixture was added N,N-dimethylacetamide (4.3 ml) and the reaction mixture was allowed to warm to 0° C. The reaction mixture was taken up into a mixture of cold water and ethyl acetate, and the pH was adjusted to around 1 with 1N hydrochloric acid. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated. The residue was chromatographed on silica gel (150 ml) eluting with a mixture of n-hexane and ethyl acetate (20:1, V/V) to give 4-Acetyl-4'-n-heptylbiphenyl (1.60 g).

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.6 Hz), 1.05–1.48 (8H, m), 1.48–1.75 (2H, m), 2.65 (2H, t, J=7.6 Hz), 2.63 (3H, s), 7.20–7.31 (2H, m), 7.52–7.58 (2H, m), 7.65–7.70 (2H, m), 7.97–8.05 (2H, m)

APCI-MASS: m/z=295 (M+1)

Preparation 312

To a solution of Methyl 4-[4-(8-hydroxyoctyloxy)phenyl] benzoate (500 mg) and dihydropyrane (141 mg) in dichloromethane (15 ml) was added p-toluenesulfonic acid (5 ml). The mixture was stirred at ambient temperature for 10 minutes and diluted with dichloromethane and washed with water and brine. The separated organic layer was dried over magnesium sulfate and evaporated under reduced pressure to give Methyl 4-[4-(8-tetrahydropyran-2-yl-oxyoctyloxy) phenyl]benzoate (616 mg).

IR (KBr): 2935, 2856, 1722, 1602, 1438, 1290, 1199 cm^{-1}

NMR ($CDCl_3$, δ): 1.3–2.0 (18H, m), 3.3–3.9 (4H, m), 3.93 (3H, s), 4.00 (2H, t, J=6.5 Hz), 4.5–4.6 (1H, m), 6.98 (2H, d, J=8.7 Hz), 7.56 (2H, d, J=8.7 Hz), 7.62 (2H, d, J=8.3 Hz), 8.07 (2H, d, J=8.3 Hz)

Preparation 313

To a solution of titanium(IV) chloride (11.6 g) in dichloromethane (100 ml) was added 4-n-Pentyloxyacetophenone (10.3 g) and Methyl 4-formylbenzoate (8.2 g) in dichloromethane (50 ml) dropwise at 0° C. To the mixture was added triethylamine (11.15 ml) in dichloromethane (30 ml). The mixture was stirred at 0° C. for 30 minutes and diluted with n-hexane. The organic layer was washed with water (four times), brine and dried over magnesium sulfate. The solvents were removed under reduced pressure and the residue was triturated with iso-propyl ether. The solid was collected by filtration and dried to give 1-(4-Methoxycarbonylphenyl)-3-(4-n-pentyloxyphenyl)-1-propene-3-one (4.02 g).

IR (KBr): 2950, 2910, 2863, 1718, 1654, 1606, 1274, 1176 cm^{-1}

NMR ($CDCl_3$, δ): 0.94 (3H, t, J=6.9 Hz), 1.3–1.6 (4H, m), 1.8–2.0 (2H, m), 3.93 (3H, s), 4.04 (2H, t, J=6.5 Hz), 6.97 (2H, d, J=8.8 Hz), 7.60 (1H, d, J=15.7 Hz), 7.68 (2H, d, J=8.4 Hz), 7.80 (1H, d, J=15.7 Hz), 8.0–8.2 (4H, m)

APCI-MASS: m/z=353 ($M+H^+$)

Preparation 314

To a solution of titanium(IV) chloride (13.88 g) in dichloromethane (100 ml) was added Ethyl 4-acetylbenzoate (11.53 g) and 4-n-pentyloxybenzaldehyde (12.69 g) in dichloromethane (50 ml) was added dropwise at 0° C. To the mixture was added triethylamine (12.44 ml) in dichloromethane (30 ml). The mixture was stirred at 0° C. for 30 minutes and diluted with ethyl acetate. The organic layer was washed with water (four times) and brine and dried over magnesium sulfate. The solvents were removed under reduced pressure and the residue was triturated with n-hexane. The solid was collected by filtration and dried to give 1-(4-n-pentyloxyphenyl)-3-(4-ethoxyoxyphenyl)-1-propene-3-one (13.45 g).

IR (KBr): 2956, 2929, 2861, 1718, 1656, 1594, 1510, 1271 cm^{-1}

NMR ($CDCl_3$, δ): 0.94 (3H, t, J=7.1 Hz), 1.3–1.9 (9H, m), 4.01 (2H, t, J=6.5 Hz), 4.42 (2H, q, J=7.1 Hz), 6.93 (1H, d, J=8.7 Hz), 7.37 (1H, d, J=15.6 Hz), 7.60 (2H, d, J=8.7 Hz), 7.81 (1H, d, J=15.6 Hz), 8.03 (2H, d, J=8.5 Hz), 8.16 (2H, d, J=8.5 Hz)

APCI-MASS: m/z=367 ($M+H^+$)

The following compound was obtained according to a similar manner to that of Preparation 314.

Preparation 315

Ethyl 4-oxo-1-(4-n-hexyloxyphenyl)piperidine-3-carboxylate

IR (Neat): 1664.3, 1511.9, 1243.9, 1216.9 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.5 Hz), 1.2–1.5 (6H, m), 1.32 (3H, t, J=7.1 Hz), 1.65–1.85 (2H, m), 2.51 (2H, t, J=5.8 Hz), 3.31 (2H, t, J=5.8 Hz), 3.76 (2H, s), 3.91 (2H, t, J=6.5 Hz), 4.26 (2H, q, J=7.1 Hz), 6.84 (2H, d, J=9.2 Hz), 6.94 (2H, d, J=9.2 Hz), 12.06 (1H, s)

APCI-MASS: m/z=348 (M^++H)

Preparation 316

To a solution of 4-n-Hexyloxybenzoylhydrazine (1.96 g) and pyridine (0.74 ml) in tetrahydrofuran (20 ml) was added a solution of terephthalic acid monomethyl ester chloride (1.56 g) in tetrahydrofuran (15 ml) dropwise at 0° C. The reaction mixture was stirred at room temperature for 2 hours, and poured into water. The precipitate was collected by filtration and washed with acetonitrile. The residue was dried under reduced pressure to give 1-(4-n-Hexyloxybenzoyl)-2-(4-methoxycarbonylbenzoyl) hydrazine (2.99 g).

IR (KBr): 3230, 3023, 2954, 2858, 1724, 1681, 1643, 1280, 1251, 1105 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.6 Hz), 1.2–1.5 (6H, m), 1.6–1.8 (2H, m), 3.90 (3H, s), 4.04 (2H, t, J=6.4 Hz), 7.04 (2H, d, J=8.7 Hz), 7.90 (2H, d, J=8.7 Hz), 8.03 (2H, d, J=8.4 Hz), 8.10 (2H, d, J=8.4 Hz), 10.42 (1H, s), 10.65 (1H, s)

APCI-MASS: m/z≦399 $(M+H)^+$

Preparation 317

A mixture of 1-(4-n-Hexyloxyphenyl)-4-piperidone (0.823 g), 1-(4-Ethoxycarbonylphenyl)piperazine (0.7 g), and titanium(IV) isopropoxide (1.11 ml) was stirred at room temperature. After 1 hour, the IR spectrum of the mixture showed no ketone band, and the viscous solution was diluted with absolute ethanol (3 ml). Sodium cyanoborohydride (0.121 g) was added, and the solution was stirred for 3 hours. Water (3 ml) was added with stirring, and the resulting in organic precipitate was filtered and washed with ethanol. The filtrate was extracted with ethyl acetate. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and filtrate was evaporated under reduced pressure to give Ethyl 4-[4-[1-(4-n-hexyloxyphenyl)piperidin-4-yl]piperazin-1-yl]benzoate (331 mg).

IR (KBr): 1708.6, 1606.4, 1511.9, 1284.4, 1236.1 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.5 Hz), 1.2–1.5 (6H, m), 1.37 (3H, t, J=7.1 Hz), 1.6–1.85 (4H, m), 1.95 (2H, d, J=12 Hz), 2.41 (1H, m), 2.62 (2H, d, J=11 Hz), 2.75 (4H, t, J=5.0 Hz), 3.35 (4H, t, J=5.0 Hz), 3.58 (2H, d, J=11 Hz), 3.90 (2H, t, J=6.5 Hz), 4.32 (2H, q, J=7.1 Hz), 6.7–7.0 (6H, m), 7.92 (2H, d, J=9.0 Hz)

APCI-MASS: m/z≦494 (M^++H)

The following compound was obtained according to a similar manner to that of Preparation 317.

Preparation 318

1-tert-Butoxycarbonyl-4-(4-phenylcyclohexyl) piperazine

IR (KBr): 1697.1, 1245.8, 1170.6, 1124.3, 700 cm^{-1}

NMR ($CDCl_3$, δ): 1.2–1.65 (17H, m), 1.9–2.1 (4H, m), 2.3–2.6 (2H, m), 2.55 (4H, t, J=5.0 Hz), 3.44 (4H, t, J=5.0 Hz), 7.1–7.4 (5H, m)

APCI-MASS: m/z=345 (M^++H)

Preparation 319

To a suspension of 1-(N,N-dimethylamino)-2-(4-ethoxycarbonylbenzoyl)ethylene (0.742 g) and 4-n-hexyloxybenzamidine hydrochloride (0.847 g) in methanol (10 ml) was added 28% sodium methoxide in methanol (0.64 ml). The suspension was refluxed for 6 hours, and partitioned with ethyl acetate and water. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with acetonitrile, collected by filtration and dried under reduced pressure to give Methyl 4-[2-(4-n-hexyloxyphenyl)pyrimidin-6-yl]benzoate (0.61 g).

IR (KBr): 2931, 2861, 1722, 1606, 1558, 1251 cm^{-1}

NMR ($CDCl_3$, δ): 0.95 (3H, t, J=6.7 Hz), 1.2–1.6 (6H, m), 1.8–2.0 (2H, m), 3.97 (3H, s), 4.05 (2H, t, J=6.5 Hz), 7.02 (2H, d, J=8.8 Hz), 7.56 (1H, d, J=5.2 Hz), 8.18 (2H, d, J=8.7 Hz), 8.28 (2H, d, J=8.6 Hz), 8.52 (2H, d, J=8.8 Hz), 8.83 (1H, d, J=5.2 Hz)

APCI-MASS: m/z=391 ($M+H^+$)

Preparation 320

A solution of 1-(4-Methoxycarbonylphenyl)-3-(4-n-pentyloxyphenyl)-1-propen-3-one (4.0 g) and hydroxyamine hydrochloride (3.93 g) in ethanol (40 ml) was refluxed for 4 hours. The mixture was diluted with ethyl acetate, and the organic layer was washed with water (×2), brine and dried over magnesium sulfate. The solvents were removed under reduced pressure to give crude oxime. To a solution of crude oxime in 1,2-dichloroethane (20 ml) was added activated-manganese(IV) oxide (10.0 g). The reaction

mixture was refluxed for 2 hours and filtered. The residue was washed with dichloromethane. The solvents were removed under reduced pressure and the residue was triturated with acetonitrile. The solid was collected by filtration and dried to give Methyl 4-[3-(4-n-pentyloxyphenyl) isoxazol-5-yl]benzoate (0.98 g).

IR (KBr): 2940, 2871, 1720, 1612, 1278, 1249, 1178, 1108 cm^{-1}

NMR (DMSO-d_6, δ): 0.94 (3H, t, J=7.2 Hz), 1.2–1.6 (4H, m), 1.7–1.9 (2H, m), 3.95 (3H, s), 4.01 (2H, t, J=6.5 Hz), 6.87 (1H, s), 6.98 (2H, d, J=8.9 Hz), 7.79 (2H, d, J=8.9 Hz), 7.89 (2H, d, J=8.6 Hz), 8.15 (2H, d, J=8.6 Hz)

APCI-MASS: m/z=366 ($M+H^+$)

Preparation 321

To a solution of 4-Methoxycarbonylphenylhydroxyiminomethyl chloride (16.98 g) and 4-n-pentyloxyphenylacetylene (18.96 g) in tetrahydrofuran (170 ml) was added triethylamine (14.4 ml) in tetrahydrofuran (140 ml) over a period of 2 hours at 40° C. and the mixture was stirred at 40° C. for 30 minutes. The mixture was diluted with dichloromethane and washed with water and brine. The separated organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with acetonitrile. The precipitate was collected by filtration and dried to give Methyl 4-[5-(4-n-pentyloxyphenyl)isoxazol-3-yl]benzoate (24.56 g).

IR (KBr): 2942, 2873, 1716, 1616, 1508, 1280, 1108 cm^{-1}

NMR ($CDCl_3$, δ): 0.95 (3H, t, J=6.9 Hz), 1.3–1.6 (4H, m), 1.8–2.0 (2H, m), 3.95 (3H, s), 4.02 (2H, t, J=6.5 Hz), 6.74 (1H, s), 6.99 (2H, d, J=8.8 Hz), 7.76 (2H, d, J=8.8 Hz), 7.93 (2H, d, J=8.5 Hz), 8.14 (2H, d, J=8.5 Hz)

APCI-MASS: m/z=366 ($M+H^+$)

Preparation 322

To a solution of N-Hydroxy-4-octyloxybenzamidine (1.89 g) in pyridine (10 ml) was added terephthalic acid monomethyl ester chloride (1.67 g) in tetrahydrofuran (15 ml) dropwise at 0° C. The mixture was stirred at room temperature for 15 minutes, and poured into water. The precipitate was collected by filtration, dried and dissolved in pyridine (10 ml). The solution was refluxed for 1 hour. The reaction mixture was diluted with ethyl acetate and washed with 1N HCl, water and brine. The separated organic layer was dried over magnesium sulfate and the solvents were removed under reduced pressure. The residue was triturated with acetonitrile and collected by filtration. The solid was dried to give Methyl 4-[3-(4-n-hexyloxyphenyl)-1,2,4-oxadiazol-5-yl]benzoate (2.27 g).

IR (KBr): 2950, 2925, 2863, 1720, 1280, 1255 cm^{-1}

NMR ($CDCl_3$, δ): 0.92 (3H, t, J=6.6 Hz), 1.2–1.9 (8H, m), 3.97 (3H, s), 4.03 (2H, d, J=6.5 Hz), 7.00 (2H, d, J=8.9 Hz), 8.09 (2H, d, J=8.9 Hz), 8.20 (2H, d, J=6.6 Hz), 8.28 (2H, d, J≦6.6 Hz)

APCI-MASS: m/z=381 $(M+H)^+$

Preparation 323

A suspension of 1-(4-n-Hexyloxybenzoyl)-2-(4-methoxycarbonylbenzoyl)hydrazine (1.00 g) in phosphorus oxychloride (5 ml) was refluxed for 1 hour. After cooling, the solution was concentrated under reduced pressure. The residue was poured into ice-water and extracted with dichloromethane. The organic layer was washed with water, brine and dried over magnesium sulfate. The solvents were removed under reduced pressure. The residue was triturated with acetonitrile, collected by filtration and dried under reduced pressure to give Methyl 4-[5-(4-n-hexyloxyphenyl)-1,3,4-oxadiazole-2-yl]benzoate (761 mg).

IR (KBr): 2954, 2854, 1724, 1612, 1494, 1280, 1249 cm^{-1}

NMR ($CDCl_3$, δ): 0.91 (3H, t, J=6.6 Hz), 1.3–1.6 (6H, m), 1.7–1.9 (2H, m), 3.96 (3H, s), 4.04 (2H, t, J=6.5 Hz), 7.02 (2H, d, J=8.6 Hz), 8.07 (2H, d, J=8.6 Hz), 8.19 (4H, m)

APCI-MASS: m/z=381 $(M+H)^+$

The following compounds (Preparation 324 to 327) were obtained according to a similar manner to that of Preparation 323.

Preparation 324

Methyl 4-[5-[4-(4-n-propyloxyphenyl)phenyl]-1,3,4-oxadiazol-2-yl]benzoate

IR (KBr): 1720, 1614, 1496, 1280, 1103 cm^{-1}

NMR ($CDCl_3$, δ): 1.07 (3H, d, J=7.5 Hz), 1.84 (2H, tq, J=6.5 and 7.5 Hz), 3.98 (3H, s), 3.99 (2H, t, J=6.5 Hz), 7.01 (2H, d, J=8.8 Hz), 7.60 (2H, d, J=8.8 Hz), 7.73 (2H, d, J=8.5 Hz), 8.19 (2H, d, J=8.5 Hz), 8.22 (4H, s)

APCI-MASS: m/z=415 ($M+H^+$)

Preparation 325

Methyl 4-[5-(n-nonyl)-1,3,4-oxadiazol-2-yl] benzoate

IR (KBr): 2915, 2848, 1724, 1569, 1436, 1413, 1278 cm^{-1}

NMR ($CDCl_3$, δ): 0.88 (3H, t, J=6.4 Hz), 1.2–1.6 (12H, m), 1.8–2.0 (2H, m), 2.94 (2H, t, J=7.6 Hz), 3.96 (3H, s), 8.11 (2H, d, J=8.8 Hz), 8.17 (2H, d, J=8.8 Hz)

APCI-MASS: m/z=331 $(M+H)^+$

Preparation 326

Methyl 4-[5-[4-(8-methoxyoctyloxy)phenyl]-1,3,4-oxadiazol-2-yl]benzoate

IR (KBr): 2925, 2858, 1722, 1614, 1280, 1259 cm^{-1}

NMR ($CDCl_3$, δ): 1.3–1.9 (12H, m), 3.36 (3H, s), 3.37 (2H, t, J=6.4 Hz), 3.97 (3H, s), 4.04 (2H, t, J=6.5 Hz), 7.02 (2H, d, J=8.9 Hz), 8.07 (2H, d, J=8.9 Hz), 8.20 (4H, s)

APCI-MASS: m/z=439 ($M+H^+$)

Preparation 327

Methyl 4-[5-(4-n-octyloxyphenyl)-1,3,4-oxadiazol-2-yl]benzoate

IR (KBr): 2923, 2856, 1722, 1614, 1496, 1282, 1103 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.8 Hz), 1.2–1.6 (10H, m), 1.7–1.9 (2H, m), 3.97 (3H, s), 4.04 (2H, t, J=6.5 Hz), 7.03 (2H, d, J=8.7 Hz), 8.07 (2H, d, J=8.7 Hz), 8.19 (4H, m)

APCI-MASS: m/z=409 ($M+H^+$)

Preparation 328

A suspension of 1-(4-Hexyloxybenzoyl)-2-(4-methoxycarbonylbenzoyl)hydrazine (1.0 g) and di-phosphorus pentasulfide (1.28 g) in tetrahydrofuran (15 ml) was stirred at room temperature for 3 hours. The mixture was diluted with water (30 ml), stirred for 30 minutes and extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated

with acetonitrile. The solid was collected by filtration and dried under reduced pressure to give Methyl 4-[5-(4-n-hexyloxyphenyl)-1,3,4-thiadiazol-2-yl]benzoate (816 mg).

IR (KBr): 2925, 2871, 1722, 1608, 1436, 1276, 1106 cm^{-1}

NMR ($CDCl_3$, δ): 0.92 (3H, t, J=6.6 Hz), 1.3–2.0 (8H, m), 3.96 (3H, s), 4.03 (2H, t, J=6.5 Hz), 6.99 (2H, d, J=8.6 Hz), 7.95 (2H, d, J=8.4 Hz), 8.16 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=397 $(M+H)^+$

The following compounds (Preparations 329 to 334) were obtained according to a similar manner to that of Preparation 328.

Preparation 329

Methyl 4-[5-[4-(8-methoxyoxyoctyloxy)pheny]-1,3,4-thiadiazol-2-yl]benzoate

IR (KBr): 3210, 2935, 2856, 1718, 1600, 1465, 1280, 1110 cm^{-1}

NMR ($CDCl_3$, δ): 1.3–1.6 (10H, m), 1.7–1.9 (2H, m), 3.33 (3H, s), 3.37 (2H, d, J=6.4 Hz), 3.96 (3H, s), 4.03 (2H, t, J=6.5 Hz), 6.99 (2H, d, J=8.9 Hz), 7.94 (2H, d, J=8.9 Hz), 8.07 (2H, d, J=8.6 Hz), 8.16 (2H, d, J=8.6 Hz)

APCI-MASS: m/z=455 $(M+H^+)$

Preparation 330

Methyl 4-[5-(4-cyclohexylphenyl)-1,3,4-thiadiazol-2-yl]benzoate

IR (KBr): 2925, 2850, 1716, 1432, 1274, 1108, 997 cm^{-1}

NMR ($CDCl_3$, δ): 1.2–1.6 (5H, m), 1.7–2.0 (5H, m), 2.58 (1H, m), 3.96 (3H, s), 7.34 (2H, d, J=8.2 Hz), 7.93 (2H, d, J=8.2 Hz), 8.07 (2H, ,d, J=8.6 Hz), 8.16 (2H, d, J=8.6 Hz)

APCI-MASS: m/z=379 $(M+H^+)$

Preparation 331

Methyl 4-[5-[4-(piperidin-1-yl)phenyl]-1,3,4-thiadiazol-2-yl]benzoate

IR (KBr): 2940, 2848, 1720, 1602, 1436, 1415, 1276, 1108 cm^{-1}

NMR ($CDCl_3$, δ): 1.68 (6H, br), 3.34 (4H, br), 3.96 (3H, s), 6.95 (2H, d, J=8.7 Hz), 7.88 (2H, d, J=8.7 Hz), 8.05 (2H, d, J=8.6 Hz), 8.16 (2H, d, J≦8.6 Hz)

APCI-MASS: m/z=380 $(M+H^+)$

Preparation 332

Methyl 4-[5-(4-n-octyloxyphenyl)-1,3,4-thiadiazol-2-yl]benzoate

IR (KBr): 2927, 2858, 1720, 1606, 1434, 1276, 1106 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.8 Hz), 1.2–1.6 (10H, m), 1.7–1.9 (2H, m), 3.96 (3H, s), 4.03 (2H, t, J=6.5 Hz), 7.00 (2H, d, J=8.9 Hz), 7.95 (2H, d, J=8.9 Hz), 8.06 (2H, d, J=8.4 Hz), 8.16 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=425 $(M+H^+)$

Preparation 333

Methyl 4-[5-(4-trans-n-pentylcyclohexyl)-1,3,4-thiadiazol-2-yl]benzoate

IR (KBr): 2923, 2850, 1722, 1440, 1276, 1116 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.9 Hz), 1.0–1.8 (13H, m), 1.92 (2H, d, J=13.4 Hz), 2.24 (2H, d, J=12.2 Hz), 3.15 (1H, tt, J=12.2 and 3.5 Hz), 3.95 (3H, s), 8.01 (2H, dd, J=8.6 and 2.0 Hz), 8.13 (2H, dd, J=8.6 and 2.0 Hz)

APCI-MASS: m/z=373 $(M+H^+)$

Preparation 334

Methyl 4-[5-[4-(4-n-propyloxyphenyl)phenyl]-1,3,4-thiadiazol-2-yl]benzoate

IR (KBr): 1720, 1540, 1508, 1282 cm^{-1}

NMR ($CDCl_3$, δ): 1.07 (3H, t, J=7.5 Hz), 1.85 (2H, m), 3.9–4.1 (5H, m), 7.01 (2H, d, J=8.8 Hz), 7.59 (2H, d, J=8.8 Hz), 7.70 (2H, d, J=8.4 Hz), 8.07 (2H, d, J=8.4 Hz), 8.1–8.2 (4H, m)

APCI-MASS: m/z=431 $(M+H)^+$

Preparation 335

To a suspension of 4-hexyloxybenzoic acid in oxalyl chloride (10 ml) and dichloromethane (10 ml) was added N,N-dimethylformamide (0.1 ml). The mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure to give crude 4-hexyloxybenzoate chloride. To a suspension of Ethyl 3-amino-4-hydroxybenzoate (733 mg) and triethylamine (1.38 ml) and 4-dimethylaminopyridine (DMAP, 10 mg) in methylene chloride (10 ml) was added the solution of 4-hexyloxybenzoyl chloride obtained above in dichloromethane (5 ml) dropwise at 10° C. The reaction mixture was stirred at 10° C. for 1.5 hours and diluted with dichloromethane (20 ml). the solution was washed with H_2O (20 ml), 1N HCl aq. (20 ml×2), H_2O (20 ml) and brine (20 ml) successively. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. To the residue was added toluene (15 ml) and p-toluenesulfonic acid (10 mg). The mixture was refluxed for 6 hours and the solvent was removed under reduced pressure. The residue was triturated with acetonitrile, and precipitate was collected with filtration and dried over PO_5 to give 2-(4-Hexyloxyphenyl)-5-ethoxycarbonylbenzoxazole (0.60 g).

IR (KBr): 2952, 2871, 1712, 1623, 1500, 1294, 1255 cm^{-1}

NMR ($CDCl_3$, δ): 0.92 (3H, t, J=6.6 Hz), 1.3–1.6 (9H, m), 1.7–1.9 (2H, m), 4.05 (2H, t, J=6.5 Hz), 4.42 (2H, q, J=7.1 Hz), 7.03 (2H, d, J=6.9 Hz), 7.57 (1H, d, J=8.6 Hz), 8.08 (1H, dd, J=8.6 and 1.7 Hz), 8.18 (2H, d, J=6.9 Hz), 8.43 (1H, d, J=1.7 Hz)

APCI-MASS: m/z=368 $(M+H^+)$

The following compounds (Preparations 336 to 337) were obtained according to a similar manner to that of Preparation 335.

Preparation 336

5-Ethoxycarbonyl-2-(2-octyloxypyridin-5-yl) benzoxazole

IR (KBr): 2933, 2858, 1716, 1623, 1604, 1577, 1467, 1290, 1213, 1083 cm^{-1}

NMR ($CDCl_3$, δ): 0.89 (3H, t, J=6.7 Hz), 1.2–1.5 (10H, m), 1.43 (3H, t, J=7.1 Hz), 1.7–1.9 (2H, m), 4.3–4.5 (4H, m), 6.87 (1H, d, J=8.7 Hz), 7.60 (1H, d, J=8.6 Hz), 8.11 (1H, dd, J=8.6 and 1.6 Hz), 8.37 (1H, dd, J=8.8 and 2.4 Hz), 8.45 (1H, d, J=1.6 Hz), 9.03 (1H, d, J=2.4 Hz)

APCI-MASS: m/z=397 $(M+H^+)$

Preparation 337

2-[4-(4-Hexylphenyl)phenyl]-5-ethoxycarbonylbenzoxazole

IR (KBr): 2952, 2871, 1712, 1623, 1500, 1294, 1255, 1024 cm^{-1}

NMR ($CDCl_3$, δ): 0.90 (3H, t, J=6.6 Hz), 1.2–1.5 (6H, m), 1.44 (3H, t, J=7.1 Hz), 1.6–1.8 (2H, m), 2.67 (2H, t, J=7.3 Hz), 4.43 (2H, q, J=7.1 Hz), 7.27 (1H, d, J=3.7 Hz), 7.32 (1H, s), 7.5–7.7 (3H, m), 7.77 (2H, d, J=8.6 Hz), 8.12 (1H, dd, J=8.6 and 1.7 Hz), 8.32 (2H, d, J=8.5 Hz), 8.48 (1H, d, J=1.2 Hz)

APCI-MASS: m/z=428 ($M+H^+$)

Preparation 338

A suspension of 4-[4-(8-bromooctyloxy)phenyl]benzoic acid (1 g) in 2,6-dimethylmorpholine (3.06 ml) was refluxed for 30 minutes. The reaction mixture was added to mixture of water and ethyl acetate and adjusted to pH 2.0 with conc. HCl. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 4-[4-[8-2,6-dimethylmorpholin-4-yl)octyloxy]phenyl] benzoic acid hydrochloride (0.95 g).

IR (KBr): 2939.0, 1704.8, 1606.4, 1189.9 cm^{-1}

NMR (DMSO-d_6, δ): 1.12 (6H, d, J=6.3 Hz), 1.2–1.6 (10H, m), 1.6–1.9 (4H, m), 2.4–2.7 (2H, m), 2.9–3.1 (2H, m), 3.8–4.0 (2H, m), 4.02 (2H, t, J=6.3 Hz), 7.04 (2H, d, J=8.8 Hz), 7.68 (2H, d, J=8.8 Hz), 7.75 (2H, d, J=8.4 Hz), 7.99 (2H, d, J=8.4 Hz)

APCI-MASS: m/z=440 ($M+H^+$)

Preparation 339

Sodium hydride (60% suspension in mineral oil, 108 mg) was added to ethoxyethanol (10 ml), and the solution was stirred at 60° C. for 20 minutes. To the solution was added Methyl 4-[4-(8-bromooctyloxy)phenyl]benzoate (1.26 g), and the reaction mixture was stirred at 70° C. for 2 hours. To the reaction mixture was added 10% sodium hydroxide aqueous solution (2.4ml), and the solution was stirred at 70° C for 1 hour. After cooling, the solution was adjusted to pH 2.0 with 1N hydrochloric acid. The precipitate was collected by filtration, and dried to give 4-[4-[8-(2-Ethoxyethoxy) octyloxy]phenyl]benzoic acid (1.13 g).

IR (KBr): 2933, 2858, 1685, 1604, 1434, 1294, 1132 cm^{-1}

NMR (DMSO-d_6, δ): 1.09 (3H, t, J=7.0 Hz), 1.2–1.9 (14H, m), 3.2–3.6 (6H, m), 4.01 (2H, d, J=6.3 Hz), 7.04 (2H, d, J=8.8 Hz), 7.67 (2H, d, J=8.8 Hz), 7.74 (2H, d, J=8.5 Hz), 7.98 (2H, d, J=8.5 Hz)

APCI-MASS: m/z=415 ($M+H^+$)

The following compound was obtained according to a similar manner of that of Preparation 300.

Preparation 340

4-n-Pentyloxybenzoylhydrazine

IR (KBr): 3182, 2937, 2869, 1645, 1618, 1571, 1251 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (3H, d, J=7.1 Hz), 1.2–1.8 (6H, m), 4.00 (2H, t, J=6.5 Hz), 4.41 (2H, s), 6.96 (2H, d, J=8.8 Hz), 7.78 (2H, d, J=8.8 Hz), 9.59 (1H, s)

APCI-MASS: m/z=223 ($M+H^+$)

The following compound was obtained according to a similar manner to that of Preparation 291.

Preparation 341

1-(4-Methoxycarbonylbenzoyl)-2-(4-n-pentyloxybenzoyl)-hydrazine

IR (KBr): 3234, 2956, 2931, 1724, 1683, 1643, 1610, 1284, 1253 cm^{-1}

NMR (DMSO-d_6, δ): 0.90 (3H, t, J=6.9 Hz), 1.2–1.5 (4H, m), 1.6–1.8 (2H, m), 3.90 (3H, s), 4.04 (2H, t, J=6.5 Hz), 7.04 (2H, d, J=8.8 Hz), 7.90 (2H, d, J=8.8 Hz), 8.03 (2H, d, J=8.7 Hz), 8.10 (2H, d, J=8.7 Hz), 10.42 (1H, s), 10.64 (1H, s)

APCI-MASS: m/z=385 ($M+H^+$)

The following compound was obtained according to a similar manner to that of Preparation 328.

Preparation 342

Methyl 4-[5-(4-n-pentyloxyphenyl)thiadiazol-2-yl] benzoate

IR (KBr): 2940, 2871, 1720, 1606, 1438, 1280 cm^{-1}

NMR ($CDCl_3$, δ): 0.95 (3H, t, J=7.1 Hz), 1.3–1.6 (4H, m), 1.8–2.0 (2H, m), 3.96 (3H, s), 4.03 (2H, t, J=6.5 Hz), 6.99 (2H, d, J=8.8 Hz), 7.94 (2H, d, J=8.8 Hz), 8.06 (2H, d, J=8.7 Hz), 8.16 (2H, d, J=8.7 Hz).

APCI-MASS: m/z=383 ($m+H^+$)

The following compound was obtained according to a silimar manner to that of Preparation 32

Preparation 343

4-[5-(4-n-Pentyloxyphenyl)thiadiazol-2-yl]benzoic acid

IR (KBr): 2954, 2867, 1687, 1602, 1432, 1294, 1255 cm^{-1}

NMR (DMSO-d_6, δ): 0.91 (3H, t, J=7.0 Hz), 1.3–1.5 (4H, m), 1.7–1.9 (2H, m), 4.07 (2H, t, J=6.7 Hz), 7.13 (2H, d, J=8.8 Hz), 7.97 (2H, d, J=8.8 Hz), 8.07 (4H, s)

APCI-MASS: m/z=369 ($M+H^+$)

The following compound was obtained according to a similar manner to that of Preparation 49.

Preparation 344

1-[4-[5-(4-n-Pentyloxyphenyl)thiadiazol-2-yl] benzoyl]-benzotriazole 3-oxide

IR (KBr): 2948, 2873, 1770, 1602, 1257, 1232 cm^{-1}

NMR ($CDCl_3$, δ): 0.95 (3H, t, J=7.1 Hz), 1.3–1.6 (4H, m), 1.8–2.0 (2H, m), 4.04 (2H, t, J=6.5 Hz), 7.01 (2H, d, J=8.1 Hz), 7.4–7.7 (3H, m) 7.97 (2H, d, J=8.1 Hz), 8.12 (1H, d, J=8.2 Hz), 8.24 (2H, d, J=8.0 Hz), 8.40 (2H, d, J=8.0 Hz)

APCI-MASS: m/z=486 ($M+H^+$)

Preparation 345

To a solution of 4-bromobenzaldehyde oxime chloride (647 mg) and 4-n-pentyloxy-phenylacetylene (650 mg) in tetrahydrofuran (7 ml) was added triethylamine (0.5 ml) in tetrahydrofuran (5 ml) dropwise at 40° C. The solution was stirred at 40° C. for 30 minutes, poured into water and extracted with ethyl acetate. The organic layer was washed with H_2O, brine and dried over magnesium sulfate. The solvents were removed under reduced pressure and the residue was triturated with acetonitrile. The precipitate was collected by filtration and dried to give 4-[5-(4-n-pentyloxyphenyl)isoxazol-3-yl]bromobenzene (0.59 g).

IR (KBr): 2948, 2867, 1612, 1430, 1255 cm $^{-1}$

NMR ($CDCl_3$, δ): 0.95 (3H, t, J=6.9 Hz), 1.3–1.6 (4H, m), 1.7–1.9 (2H, m), 4.01 (2H, t, J=6.5 Hz), 6.66 (1H, s), 6.98 (2H, d, J=8.8 Hz), 7.60 (2H, d, J=8.6 Hz), 7.7–7.9 (4H, m)

APCI-MASS: m/z =388 ($M+H^{30}$)

Preparation 346

To a suspension of 4-[5-(4-n-pentyloxyphenyl)isoxazol-3-yl]bromobenzene (386 mg) in tetrahydrofuran (5 ml) was added 1.55M n-butyllithium in hexane (0.84 ml) at −40° C. under N_2 stream and the solution was stirred for 1 hour at −40° C. To the solution was added crushed dryice (1 g) and the suspension was stirred for 1 hour at −40° C. The suspension was diluted with H_2O, and acidified with 1N-hydrochloric acid. The precipitate was collected by filtration and dried to give 4-[5-(4-n-pentyloxyphenyl) isoxazol-3-yl]benzoic acid (312 mg).

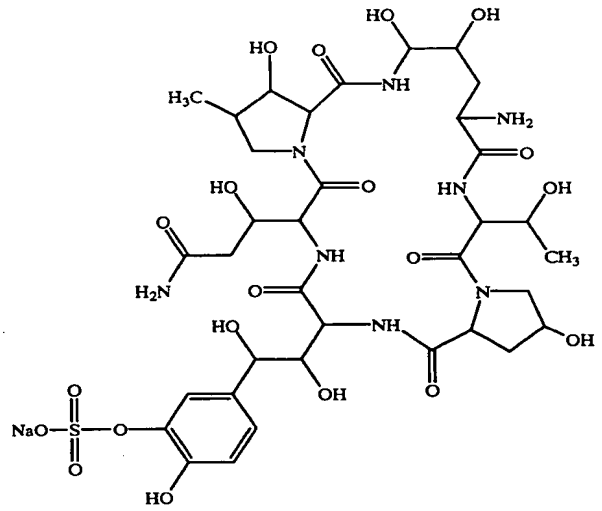
IR (KBr): 2939, 2867, 1681, 1614, 1429, 1255, 1178, 821 cm^{-1}

NMR (DMSO-d_6, δ): 0.91 (3H, t, J=7.1 Hz), 1.3–1.5 (4H, m), 1.6–1.8 (2H, m), 4.04 (2H, t, J=6.5 Hz), 7.11 (2H, d, J=8.9 Hz), 7.54 (1H, s), 7.85 (2H, d, J=8.9 Hz), 7.98 (2H, d, J=8.6 Hz), 8.11 (2H, d, J=8.6 Hz)

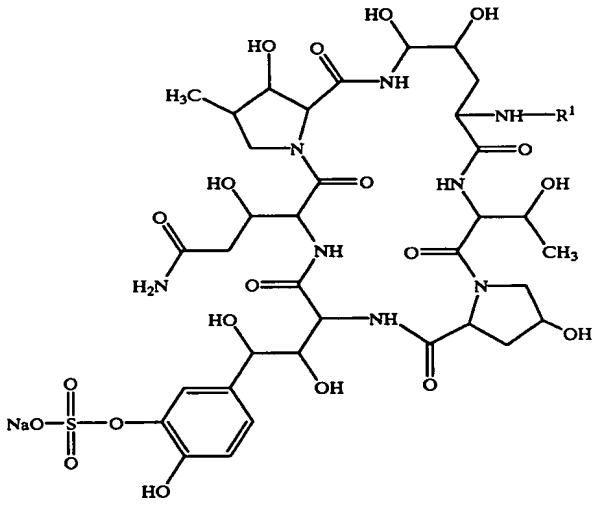
APCI-MASS: m/z=352 $M+H^+$).

The Starting Compound in the following Examples 1 to 117 and The Object Compounds (1) to (122) and (124) in the following Examples 1 to 122 and 124 are illustrated by chemical formulae as below.

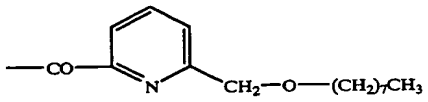
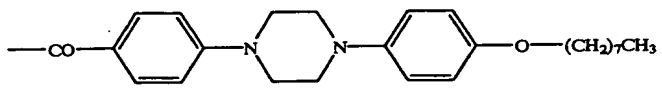
The Starting Compound (SEQ ID NO:1) (the same in Examples 1 to 117)



The Object Compounds (1) to (122) and (124) (SEQ ID NO: 1)

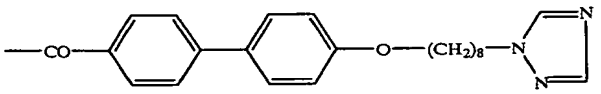


In the following Examples, The Object Compound (X) [e.g. The Object Compound (1)] means the object compound of Example (X) [e.g. Example (1)].

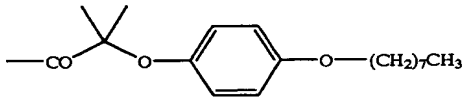
Example No.	R^1
1	
2	

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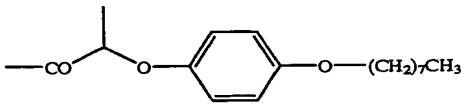
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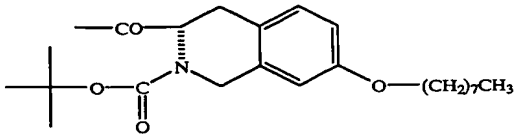
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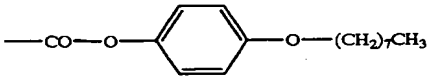
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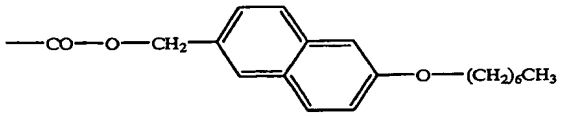
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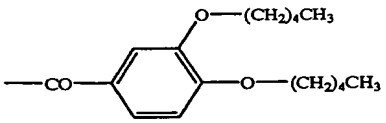
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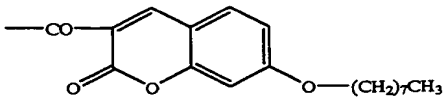
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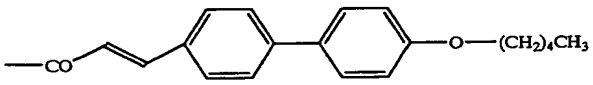
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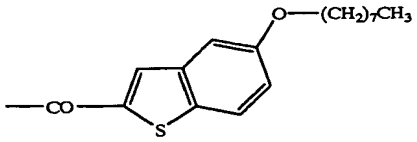
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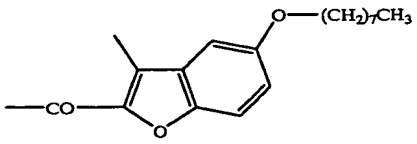
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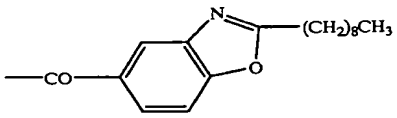
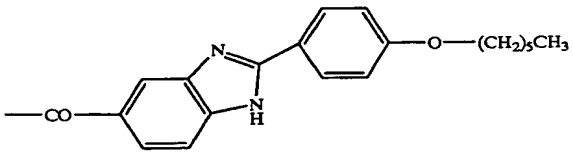
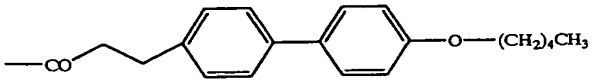
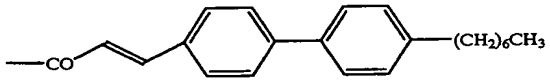
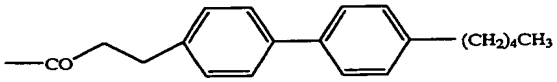
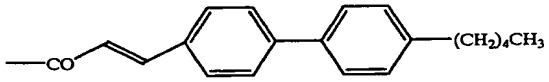
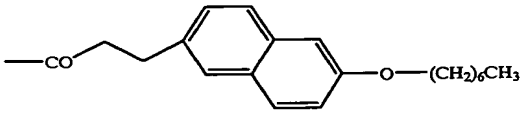
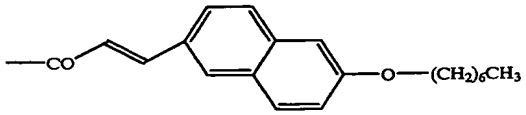
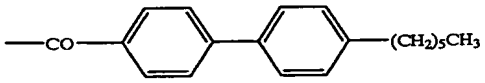
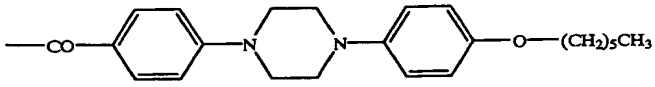
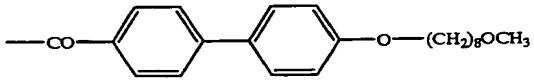
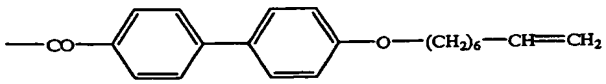
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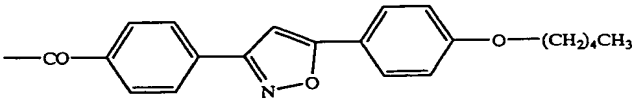


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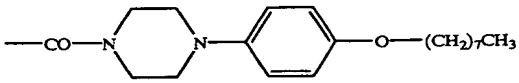
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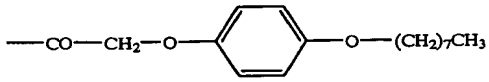
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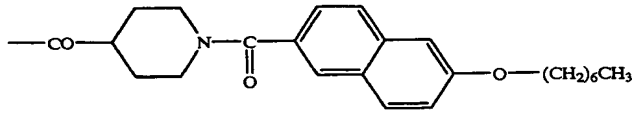
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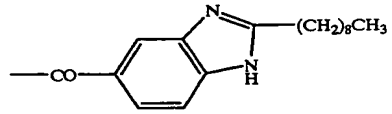
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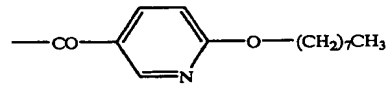
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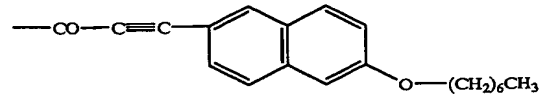
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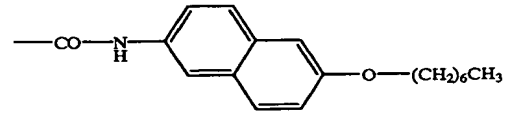
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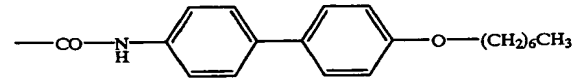
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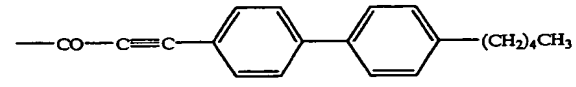
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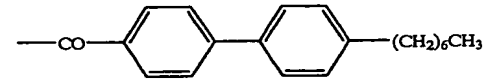
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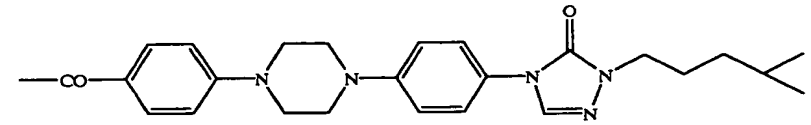
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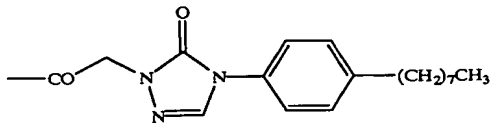


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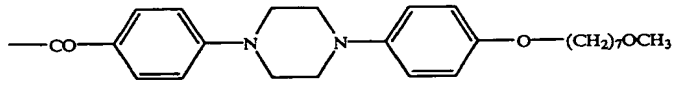


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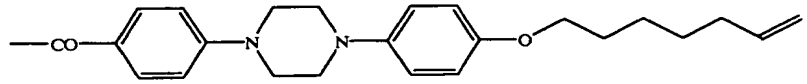
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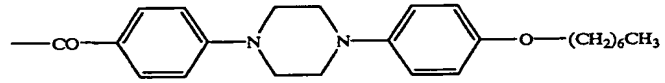
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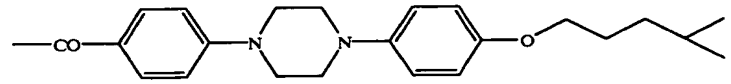
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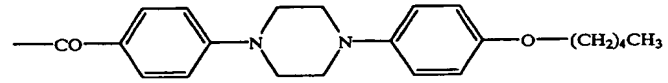
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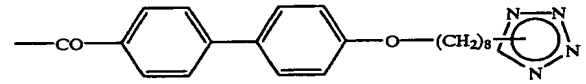
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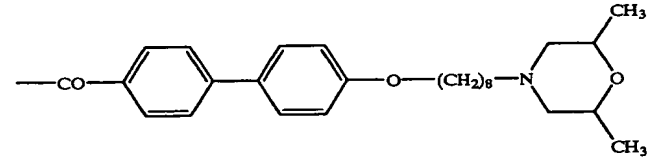
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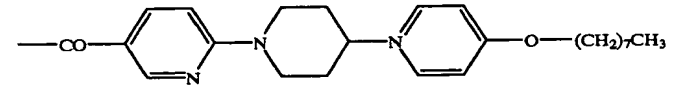
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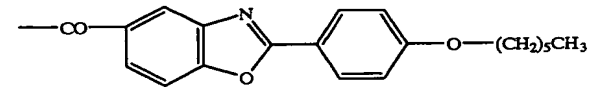
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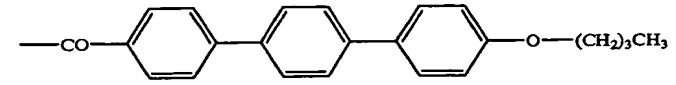
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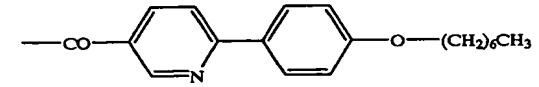
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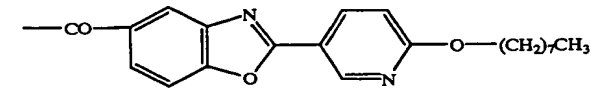
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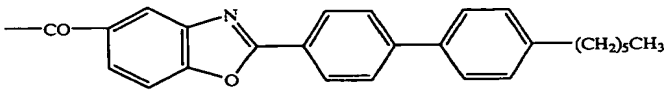


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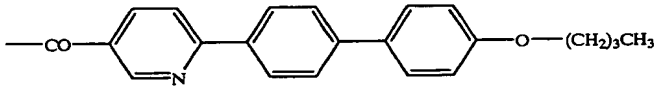


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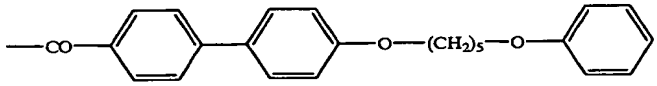
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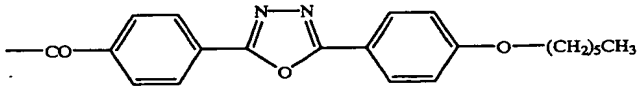
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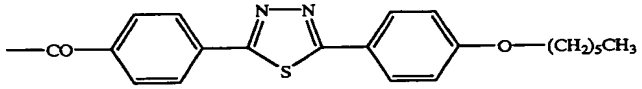
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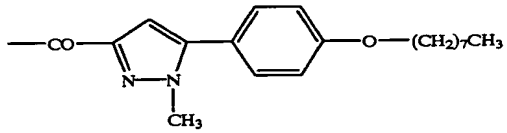
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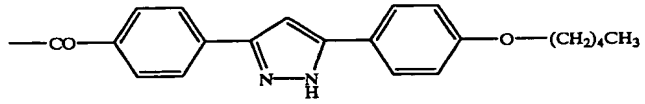
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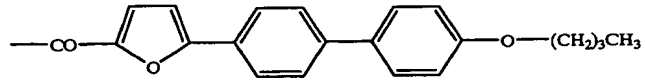
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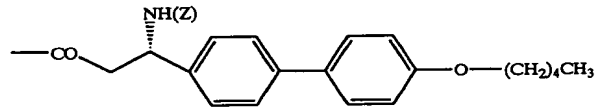
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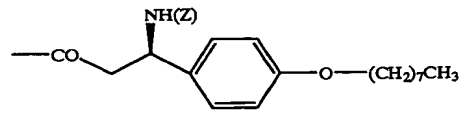
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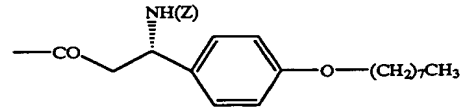
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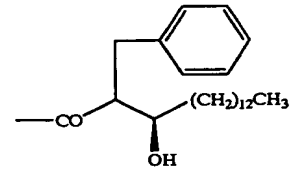
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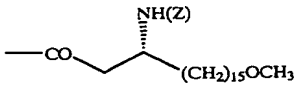


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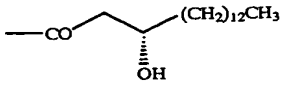


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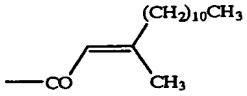
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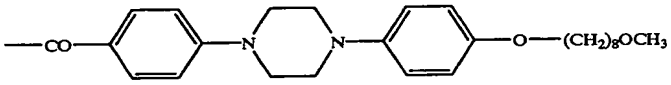
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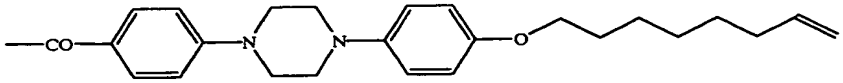
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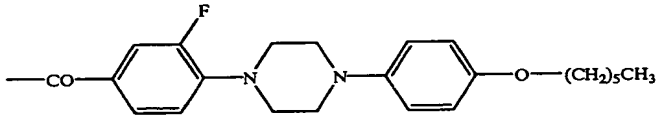
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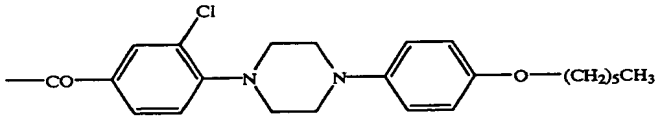
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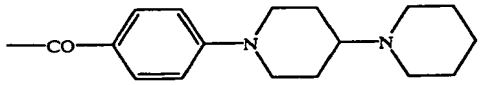
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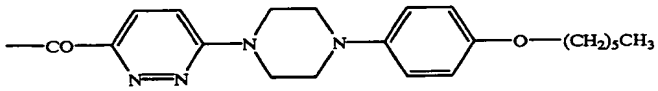
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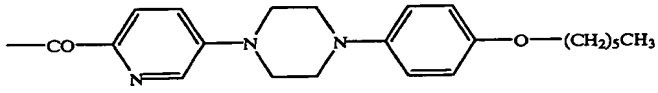
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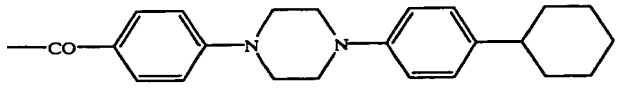
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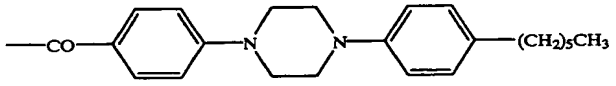
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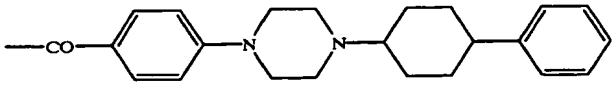
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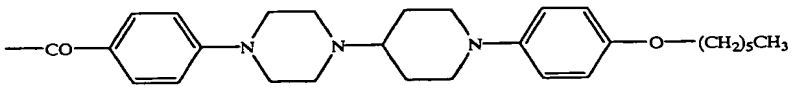


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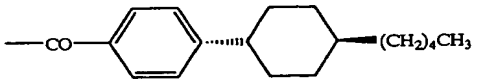


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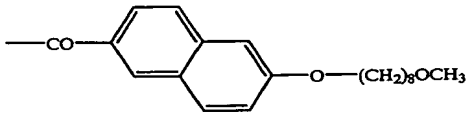
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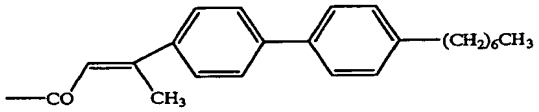
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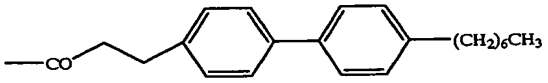
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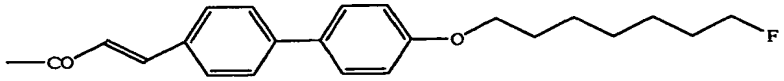
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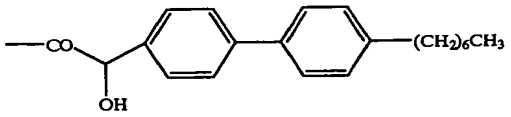
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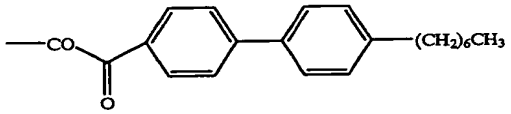
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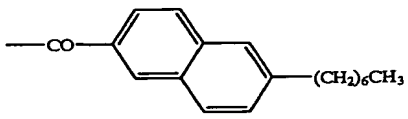
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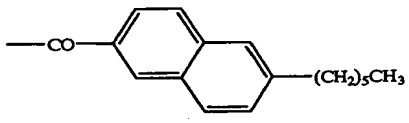
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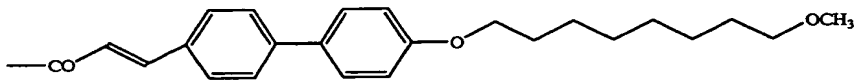
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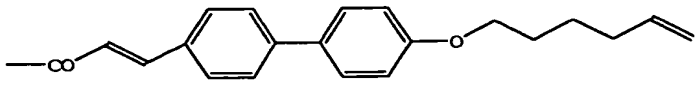
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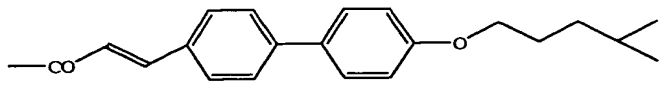
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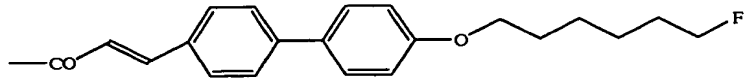


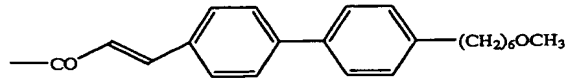
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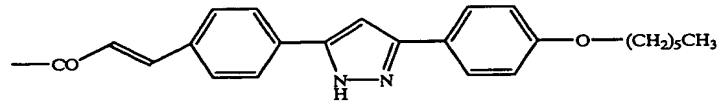


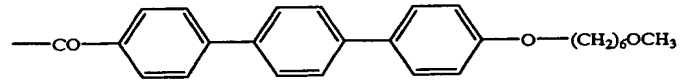
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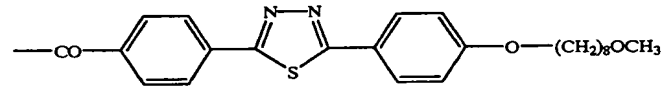
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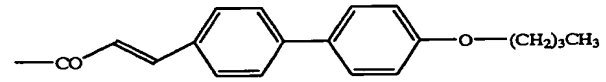
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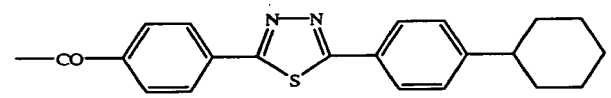
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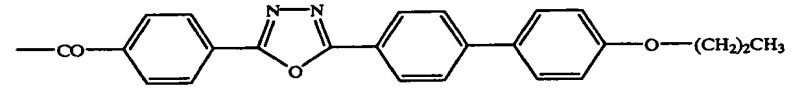
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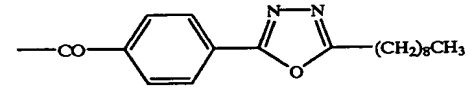
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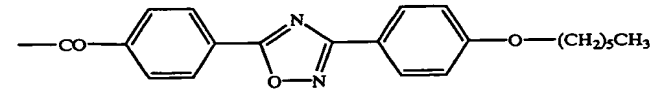
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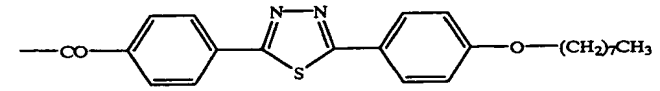
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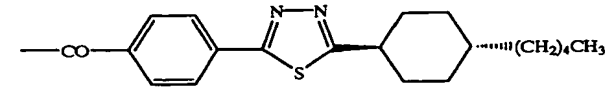
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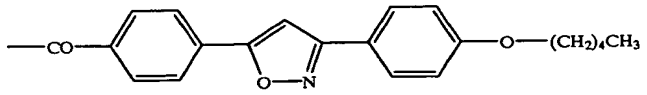
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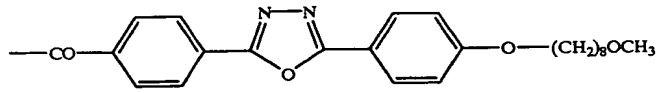
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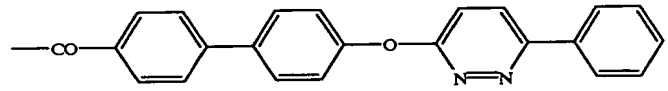
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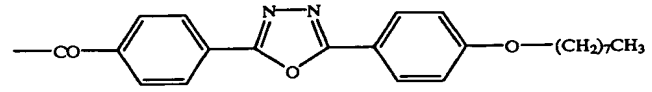
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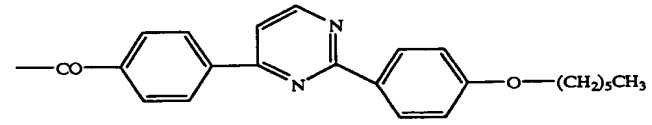
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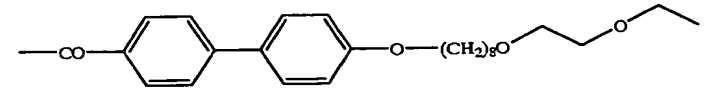
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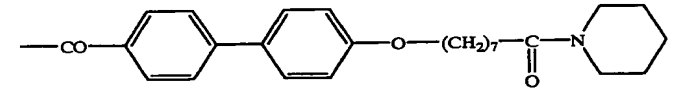
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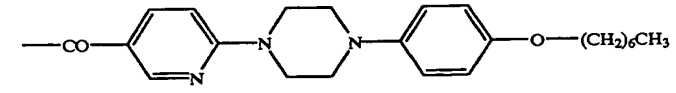
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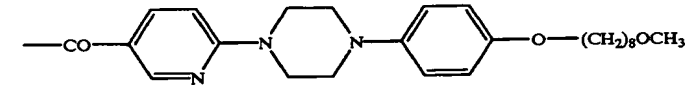
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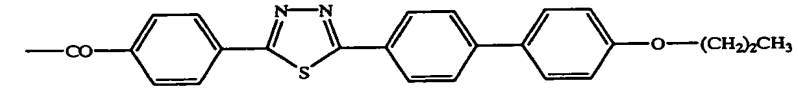
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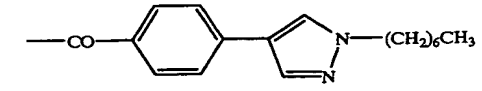
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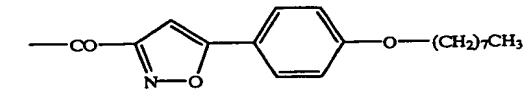
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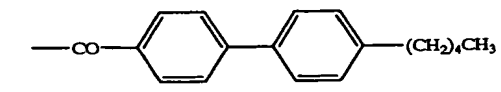
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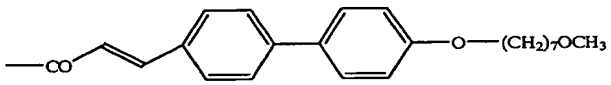
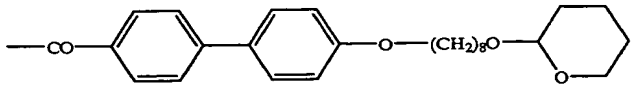
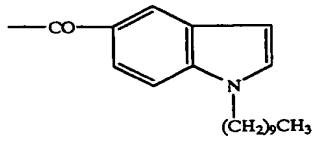
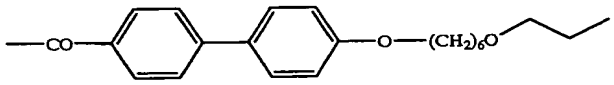
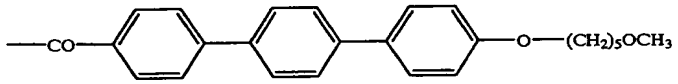
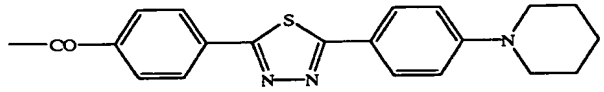
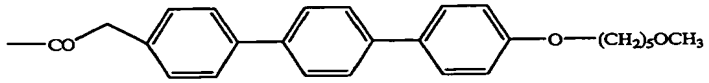
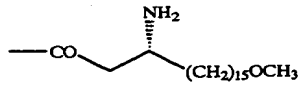
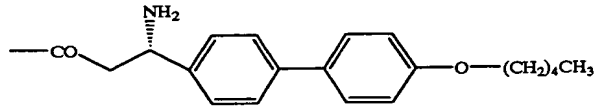
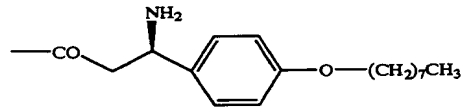
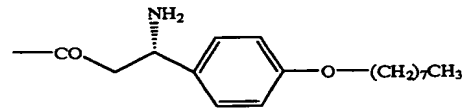
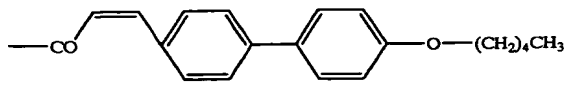
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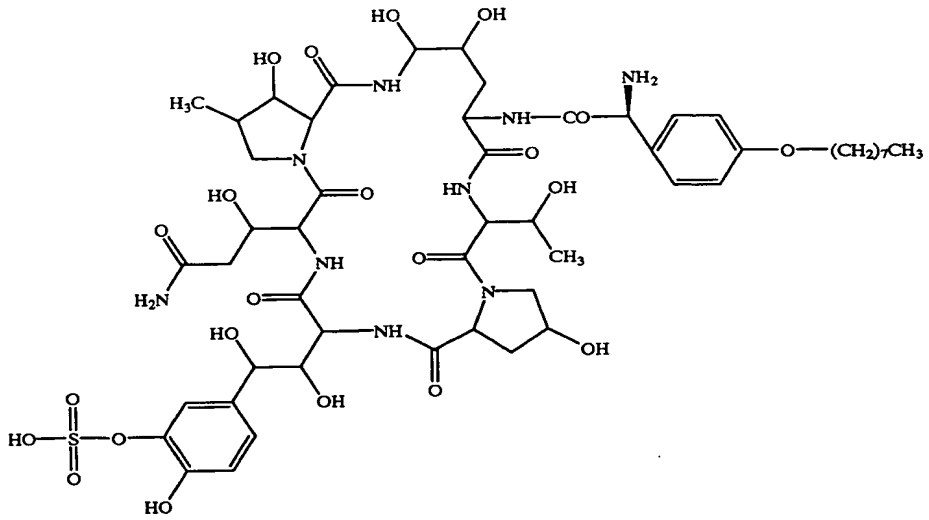
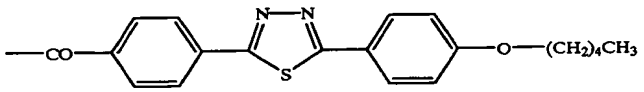
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Example No.	The Object Compound
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-continued

Example No.	R^1
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EXAMPLE 1

To a solution of The Starting Compound (1 g) and 1-(6-octyl-oxymethylpicolinoyl)benzotriazole 3-oxide (0.399 g) in N,N-dimethylformamide (10 ml) was added 4-(N,N-dimethylamino)pyridine (0.140 g), and stirred for 12 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration, and dried under reduced pressure. The powder was dissolved in water, and subjected to column chromatography on ion exchange resin (DOWEX-50WX4 (Trademark: prepared by Dow Chemical)) eluting with water. The fractions containing the object compound were combined, and subjected to column chromatography of ODS (YMC-gel.ODS-AM.S-50) Trademark: prepared by Yamamura Chemical Lab.) eluting with 50% methanol aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove methanol. The residue was lyophilized to gice The Object Compound (1).

IR (KBr): 3347, 1664, 1629, 1517 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 0.98 (3H, d, J=6.7 Hz), 1.09 (3H, d, J=6.0 Hz), 1.2–1.47 (10H, m), 1.47–1.67 (2H, m), 1.67–2.06 (3H, m), 2.06–2.5 (4H, m), 3.19 (1H, m), 3.53 (2H, t, J=6.4 Hz), 3.5–3.85 (2H, m), 3.85–4.7 (13H, m), 5.35 (11H, m), 5.56 (1H, d, J=5.7 Hz), 6.73 (1H, d, J=8.3 Hz), 6.83 (1H, d, J=8.3 Hz), 6.89 (1H, s), 7.05 (1H, s), 7.11 (1H, s), 7.32 (1H, m), 7.43 (1H, d, J=8.5 Hz), 7.63 (1H, d, J=7.3 Hz), 7.85–8.13 (4H, m), 8.66 (1H, d, J=7.8 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1228 (M^++Na)

Elemental Analysis Calcd. for $C_{50}H_{72}N_9O_{22}SNa.6H_2O$: C 45.49, H 6.44, N 9.59 Found: C 45.89, H 6.52, N 9.69

The Object Compounds (2) to (25) were obtained according to a similar manner to that of Example 1.

EXAMPLE 2

IR (KBr): 3353, 1666, 1510, 1236 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.06 (3H, d, J=5.8 Hz), 1.2–1.5 (10H, m), 1.55–2.05 (5H, m), 2.11–2.7 (4H, m), 3.0—3.3 (5H, m), 3.3–3.5 (4H, m), 3.6–4.5 (15H, m), 4.6–5.6 (12H, m), 6.6–7.2 (10H, m), 7.2–7.5 (3H, m), 7.81 (2H, d, J=8.8 Hz), 8.05 (1H, d, J=8.7 Hz), 8.28 (1H, d, J=8.7 Hz), 8.41 (1H, d, J=6.7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1373 (M^++Na)

Elemental Analysis Calcd. for $C_{60}H_{83}N_{10}O_{22}SNa.4H_2O$: C 50.63, H 6.44, N 9.84 Found: C 50.59, H 6.59, N 9.79

EXAMPLE 3

IR (KBr): 3350, 1664, 1627, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.6 Hz), 1.08 (3H, d, J=5.7 Hz), 1.15–1.53 (8H, m), 1.55–2.1 (9H, m), 2.1–2.45 (3H, m), 2.5–2.7 (1H, m), 3.18 (1H, m), 3.6–3.83 (2H, m), 3.83–4.6 (17H, m), 4.7–5.4 (11H, m), 5.51 (1H, d, J=5.9 Hz), 6.73 (1H, d, J=8.2 Hz), 6.83 (1H, d, J=8.2 Hz), 6.85 (1H, s), 7.03 (2H, d, J=8.4 Hz), 7.05 (1H, s), 7.30 (1H, s), 7.2–7.5 (2H, m), 7.67 (2H, d, J=8.4 Hz), 7.71 (2H, d, J=7.4 Hz), 7.94 (1H, s), 7.96 (2H, d, J=7.4 Hz), 8.06 (1H, d, J=8.0 Hz), 8.25 (1H, d, J=6.7 Hz), 8.50 (1H, s), 8.74 (1H, d, J=6.7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1356 (M^++Na)

Elemental Ananysis Calcd. for $C_{58}H_{76}N_{11}O_{22}SNa.4H_2O$: C 49.53, H 6.02, N10.95 Found: C 49.26, H 6.22, N 10.77

EXAMPLE 4

IR (KBr): 3350, 1660, 1631, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.9 Hz), 0.97 (3H, d, J=6.6 Hz), 1.09 (3H, d, J=5.3 Hz), 1.2–1.5 (10H, m), 1.37 (6H, s), 1.55–2.0 (5H, m), 2.1–2.6 (4H, m), 3.16 (1H, m), 3.73 (2H, m), 3.89 (2H, t, J=6.3 Hz), 3.95–4.49 (11H, m), 4.68–5.21 (10H, m), 5.25 (1H, d, J=4.1 Hz), 5.53 (1H, d, J=5.7 Hz), 6.73 (1H, d, J=8.2 Hz), 6.75–6.85 (4H, m), 6.91 (1H, d, J=8.2 Hz), 7.05 (1H, s), 7.15 (1H, s), 7.3–7.5 (2H, m), 7.9–8.2 (3H, m), 8.84 (1H, s)

FAB-MASS: m/z=1271 (M^++Na)

Elemental Analysis Calcd. For $C_{53}H_{77}N_8O_{23}SNa.4H_2O$: C 48.18, H 6.48, N 8.48 Found: C 48.04, H 6.51, N 8.38

EXAMPLE 5

IR (KBr): 1666, 1629, 1222 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.6 Hz), 0.9–1.12 (6H, m), 1.12–1.52 (13H, m), 1.52–1.93 (5H, m), 2.08–2.55 (4H, m), 3.16 (1H, m), 3.6–5.3 (26H, m), 5.49+5.54 (1H, d, J=5.8 Hz, mixture of diastereomer), 6.60–7.1 (7H, m), 7.04 (1H, s), 7.1 (1H, m), 7.2–7.5 (2H, m), 7.9–8.43 (3H, m), 8.83 (1H, s)

FAB-MASS: m/z=1257 (M^++Na)

Elemental Analysis Calcd. for $C_{52}H_{75}N_8O_{23}SNa.3H_2O$: C 48.44, H 6.33, N 8.69 Found: C 48.16, H 6.51, N 8.53

EXAMPLE 6

IR (KBr): 3349, 1666, 1629, 1259 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 0.9 (3H, d, J=5.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.1–1.55 (19H, m), 1.55–2.0 (5H, m), 2.0–2.47 (4H, m), 2.65–3.25 (3H, m), 3.5–5.13 (27H, m), 5.17 (1H, d, J=3.2 Hz), 5.24 (1H, d, J=4.5 Hz), 5.38 (1H, d, J=5.9 Hz), 6.5–6.9 (5H, m), 6.9–7.1 (3H, m), 7.2–7.46 (2H, m), 7.7–8.1 (3H, m), 8.83 (1H, s)

FAB-MASS: m/z=1368 (M^{30}+Na)

Elemental Analysis Calcd. for $C_{58}H_{84}N_9O_{24}SNa.5H_2O$: C 48.50, N 6.60, N 8.78 Found: C 48.47, H 6.83, N 8.78

EXAMPLE 7

IR (KBr): 3350, 1666, 1502, 1199 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.6 Hz), 0.97 (3H, d, J=6.7 Hz), 1.06 (3H, d, J=5.7 Hz), 1.2–1.5 (10H, m), 1.55–2.0 (5H, m), 2.1–2.6 (4H, m), 3.17 (1H, m), 3.7–4.5 (15H, m), 4.7–5.22 (10H, m), 5.24 (1H, d, J=4.4 Hz), 5.60 (1H, d, J=5.9 Hz), 6.68–7.03 (8H, m), 7.04 (1H, s), 7.2–7.42 (2H, m), 7.85–8.1 (3H, m), 8.83 (1H, s)

FAB-MASS: m/z=1229 (M^++Na)

Elemental Analysis Calcd. for $C_{50}H_{71}N_8O_{23}SNa.5H_2O$: C 46.29, H 6.29, N 8.64 Found: C 46.39, H 6.05, N 8.72

EXAMPLE 8

IR (KBr): 3350, 1666, 1631, 1513 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.2 Hz), 0.97 (3H, d, J=6.7 Hz), 1.04 (3H, d, J=5.7 Hz), 1.2–1.58 (8H, m), 1.58–2.0 (5H, m), 2.0–2.6 (4H, m), 3.17 (1H, m), 3.6–4.5 (15H, m), 4.63–5.33 (13H, m), 5.53 (1H, d, J=5.9 Hz), 6.73 (1H, d, J=8.2 Hz), 6.82 (1H, d, J=8.2 Hz), 6.84 (1H, s), 6.95–7.52 (7H, m), 7.66 (1H, d, J=7.6 Hz), 7.7–7.9 (3H, m), 8.05 (1H, d, J=9.1 Hz), 8.15 (1H, d, J=7.6 Hz), 8.85 (1H, s)

FAB-MASS: m/z=1279 (M^++Na)

Elemental Analysis Calcd. for $C_{54}H_{73}N_8O_{23}SNa.5H_2O$: C 48.14, H 6.21, N 8.32 Found: C 48.43, H 6.28, N 8.30

EXAMPLE 9

IR (KBr): 3347, 2956, 1664, 1633, 1508, 1444, 1268, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.9–1.1 (9H, m), 1.06 (3H, d, J=5.9 Hz), 1.3–1.5 (8H, m), 1.6–2.0 (7H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.3 (1H, m), 3.6–4.4 (17H, m), 4.7–5.0 (8H, m), 5.09 (1H, d, J=5.5 Hz), 5.16 (1H, d, J=3.1 Hz), 5.24 (1H, d, J=4.5 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–6.9 (2H, m), 6.98 (1H, d, J=8.3 Hz), 7.05 (1H, d, J=1.7 Hz), 7.3–7.6 (5H, m), 8.08 (1H, d, J=8.9 Hz), 8.25 (1H, d, J=8.4 Hz), 8.54 (1H, d, J=7.5 Hz), 8.83 (1H, s)

FAB-MASS: m/z=1257 (M^++Na)

Elemental Analysis Calcd. for $C_{52}H_{75}N_8O_{23}SNa.4H_2O$: C 47.78, H 6.40, N 8.57 Found: C 47.88, H 6.71, N 8.53

EXAMPLE 10

IR (KBr): 3350, 2931, 1664, 1625, 1529, 1440, 1276, 1226, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.8 Hz), 0.97 (3H, d, J=6.7 Hz), 1.12 (3H, d, J=5.9 Hz), 1.2–1.5 (10H, m), 1.6–2.1 (5H, m), 2.1–2.4 (4H, m) 3.1–3.3 (1H, m), 3.5–4.6 (15H, m), 4.7–5.0 (3H, m), 5.0–5.2 (7H, m), 5.27 (1H, d, J=4.4 Hz), 5.55 (1H, d, J=5.7 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–7.0 (2H, m), 7.0–7.2 (4H, m), 7.3–7.6 (2H, m), 7.90 (1H, d, J=8.8 Hz), 8.0–8.2 (2H, m), 8.8–8.9 (2H, m), 9.06 (1H, d, J=7.2 Hz)

FAB-MASS: m/z=1281 (M^++Na)

Elemental Analysis Calcd. for $C_{53}H_{71}N_8O_{24}SNa.5H_2O$: C 47.18, H 6.05, N 8.30 Found: C 46.97, H 6.27, N 8.22

EXAMPLE 11

NMR (DMSO-d_6, δ): 0.87–1.05 (6H, m), 1.10 (3H, d, J=5.7 Hz), 1.3–1.5 (4H, m), 1.6–1.9 (5H, m), 2.2–2.5 (3H, m), 2.6 (1H, m), 3.1–3.2 (1H, m), 3.7–4.5 (15H, m), 4.8–5.1 (8H, m), 5.09 (1H, d, J=5.64 Hz), 5.16 (1H, d, J=3.2 Hz), 5.26 (1H, d, J=4.2 Hz), 5.52 (1H, d, J=6.0 Hz), 6.73 (2H, d, J=8.4 Hz), 6.8–6.9 (2H, m), 7.0–7.1 (3H, m), 7.2–7.4 (4H, m), 7.6–7.8 (6H, m), 8.11 (1H, d, J=8.4Hz), 8.29 (1H, d, J=8.4 Hz), 8.51 (1H, d, J=7.7 Hz), 8.85 (1H, s)

FAB-MASS: m/z=1273 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{71}N_8O_{22}SNa.4H_2O$: C 49.92, H 6.02, N 8.47 Found: C 49.79, H 6.14, N 8.45

EXAMPLE 12

IR (KBr): 3330, 2929, 1670, 1629, 1533, 1440, 1280, 1226, 1045, 804 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 0.97 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.9 Hz), 1.2–1.6 (10H, m), 1.6–2.0 (5H, m), 2.1–2.5 (4H, m), 3.1–3.3 (1H, m), 3.6–4.5 (15H, m), 4.8–5.1 (9H, m), 5.17 (1H, d, J=3.0 Hz), 5.25 (1H, d, J=4.5 Hz), 5.56 (1H, d, J=5.6 Hz), 6.73 (1H, d, J=8.2 Hz), 6.83 (1H, d, J=6.8 Hz), 7.1–7.2 (3H, m), 7.3–7.5 (3H, m), 7.85 (1H, d, J=8.8 Hz), 8.0–8.2 (3H, m), 8.84 (1H, s), 8.96 (1H, d, J=7.2 Hz)

FAB-MASS: m/z=1269 (M^++Na)

Elemental Analysis Calcd. for $C_{52}H_{71}N_8O_{22}S_2Na.4H_2O$: C 47.34, H 6.04, N 8.49 Found: C 47.21, H 5.96, N 8.41

EXAMPLE 13

IR (KBr): 3345, 2927, 1664, 1629, 1515, 1442, 1274, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.7 Hz), 0.97 (3H, d, J=6.7 Hz), 1.10 (3H, d, J=5.9 Hz), 1.2–1.4 (10H, m), 1.5–2.5

(8H, m), 2.46 (3H, s), 2.69 (2H, t, J=7.7 Hz), 3.1–3.4 (2H, m), 3.6–4.5 (17H, m), 4.8–5.2 (8H, m), 6.7–7.0 (3H, m), 7.05 (1H, d, J=1.7 Hz), 7.14 (1H, s), 7.3–7.6 (5H, m), 8.0–8.2 (2H, m), 8.47 (1H, d, J=7.0 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1251 (M^++Na)

Elemental Analysis Calcd. for $C_{53}H_{73}N_8O_{22}SNa.3H_2O$: C 49.61, H 6.21, N 8.73 Found: C 49.88, H 6.44, N 8.74

EXAMPLE 14

IR (KBr): 3340, 1672, 1627, 1542, 1513, 1440, 1268, 1045 cm^{-1}

NMR (DMSO-d_6, δ): 0.84 (3H, t, J=6.7 Hz), 0.94 (3H, d, J=6.7 Hz), 1.07 (3H, d, J=6.0 Hz), 1.2–1.4 (12H, m), 1.6–2.0 (5H, m), 2.1–2.4 (3H, m), 2.6 (1H, m), 2.96 (2H, t, J=7.4 Hz), 3.1–3.3 (1H, m), 3.6–4.5 (13H, m), 4.7–5.2 (11H, m), 5.50 (1H, d, J=5.7 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–6.9 (2H, m), 7.04 (1H, s), 7.2–7.5 (3H, m), 7.72 (1H, d, J=8.5 Hz), 7.91 (1H, d, J=8.4 Hz), 8.05 (1H, d, J=8.4 Hz), 8.2–8.4 (1H, m), 8.80 (1H, d, J=7.7 Hz), 8.83 (1H, s)

FAB-MASS: m/z=1252 (M^++Na)

Elemental Analysis Calcd. for $C_{52}H_{72}N_9O_{22}SNa.6H_2O$: C 46.67, H 6.33, N 9.42 Found: C 46.72, H 6.53, N 9.45

EXAMPLE 15

IR (KBr): 3350, 2935, 1664, 1627, 1517, 1446, 1251, 1045 cm^{-1}

NMR (DMSO-d_6, δ): 0.90–1.1 (6H, m), 1.10 (3H, d, J=5.9 Hz), 1.2–1.4 (6H, m), 1.6–2.4 (8H, m), 2.6–2.7 (1H, m), 3.1–3.3 (1H, m), 3.7–4.5 (16H, m), 4.7–5.4 (11H, m), 5.51 (1H, d, J=5.6 Hz), 6.7–7.0 (3H, m), 7.0–7.6 (7H, m), 7.74 (1H, d, J=8.6 Hz), 8.0–8.4 (5H, m), 8.7–8.8 (1H, m), 8.84 (1H, s)

FAB-MASS: m/z=1301 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{71}N_{10}O_{22}SNa.6H_2O$: C 47.62, H 6.03, N 10.01 Found: C 47.65, H 6.03, N 10.03

EXAMPLE 16

IR (Nujol): 3353, 1668, 1627, 1540, 1515, 1500 cm^{-1}

NMR (DMSO-d_6, δ): 0.80–1.00 (6H, m), 1.06 (3H, d, J=5.9 Hz), 1.20–1.53 (4H, m), 1.60–1.95 (5H, m), 2.00–2.65 (8H, m), 2.80 (2H, t, J=7.5 Hz), 3.05–3.45 (1H, m), 3.50–3.85 (2H, m), 3.90–4.48 (11H, m), 4.65–5.38 (11H, m), 5.47 (1H, d, J=6.0 Hz), 6.65–6.90 (2H, m), 6.90–7.10 (2H, m), 7.10–7.65 (11H, m), 7.90–8.25 (2H, m), 8.30 (1H, d, J=7.8 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1275.3 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{73}N_8O_{22}SNa.3H_2O$: C 50.53, H 6.09, N 8.57 Found: C 50.48, H 6.39, N 8.57

EXAMPLE 17

IR (Nujol): 3351, 1656, 1623, 1538, 1515 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.8 Hz), 1.15–1.40 (8H, m), 1.50–2.00 (5H, m), 2.10–2.48 (4H, m), 2.52–2.70 (2H, m), 3.05–3.28 (1H, m), 3.60–4.50 (13H, m), 4.70–5.20 (9H, m), 5.25 (1H, d, J=4.6 Hz), 5.52 (1H, d, J=6.0 Hz), 6.68–6.92 (4H, m), 7.04 (1H, d, J=1.0 Hz), 7.22–7.50 (5H, m), 7.55–7.82 (7H, m), 8.14 (1H, d, J=8.4 Hz), 8.31 (1H, d, J=8.4 Hz), 8.54 (1H, d, J=7.7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1285 (M^++Na)

EXAMPLE 18

IR (Nujol): 3351, 1668, 1627, 1540, 1515 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.8 Hz), 0.96 (3H, d, J=6.7 Hz), 1.06 (3H, d, J=5.8 Hz), 1.17–1.48 (4H, m), 1.50–1.95 (5H, m), 2.05–2.70 (8H, m), 2.70–2.95 (2H, m), 3.05–3.30 (1H, m), 3.60–3.90 (2H, m), 3.90–4.50 (11H, m), 4.65–5.10 (9H, m), 5.15 (1H, d, J=3.2 Hz), 5.23 (1H, d, J=4.2 Hz), 5.48 (1H, d, J=6.0 Hz), 6.67–6.90 (3H, m), 7.03 (1H, d, J=1.5 Hz), 7.15–7.80 (11H, m), 8.00–8.20 (2H, m), 8.29 (1H, d, J=7.8 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1259 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{73}N_8O_{21}SNa.6H_2O$: C 50.30, H 6.52, N 8.53 Found: C 50.42, H 6.50, N 8.45

EXAMPLE 19

IR (Nujol): 3351, 1668, 1652, 1623, 1540 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.07 (3H, d, J=6.0 Hz), 1.25–1.45 (4H, m), 1.50–2.00 (5H, m), 2.05–2.48 (4H, m), 2.50–2.75 (2H, m), 3.60–4.50 (13H, m), 4.68–5.25 (10H, m), 5.27 (1H, d, J=4.5 Hz), 5.53 (1H, d, J=6.0 Hz), 6.67–6.98 (4H, m), 7.05 (1H, d, J=1.0 Hz), 7.22–7.58 (5H, m), 7.58–7.90 (7H, m), 8.16 (1H, d, J=9.0 Hz), 8.34 (1H, d, J=8.4 Hz), 8.57 (1H, d, J=7.7 Hz), 8.85 (1H, s)

FAB-MASS: m/z=1258 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{71}N_8O_{21}SNa.5H_2O$: C 49.84, H 6.15, N 8.45 Found: C 49.77, H 6.27, N 8.39

EXAMPLE 20

IR (Nujol): 3353, 1670, 1629, 1540, 1508 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.5 Hz), 0.97 (3H, d, J=6.8 Hz), 1.04 (3H, d, J=5.9 Hz), 1.20–1.58 (8H, m), 1.60–1.96 (5H, m), 2.08–2.60 (6H, m), 2.70–3.00 (2H, m), 3.00–3.40 (1H, m), 3.60–3.85 (2H, m), 3.85–4.50 (13H, m), 4.50–5.60 (12H, m), 6.65–6.90 (3H, m), 7.00–7.15 (3H, m), 7.18–7.50 (4H, m), 7.59 (1H, s), 7.62–7.78 (2H, m), 7.95–8.20 (2H, m), 8.30 (1H, d, J=7.7 Hz), 8.83 (1H, s)

FAB-MASS: m/z=1277 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{75}N_8O_{22}SNa.4H_2O$: C 49.77, H 6.30, N 8.44 Found: C 49.67, H 6.31, N 8.40

EXAMPLE 21

IR (Nujol): 3351, 1654, 1623, 1538, 1515 $cm^{31\ 1}$

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.7 Hz), 0.97 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.9 Hz), 1.20–1.58 (8H, m), 1.66–1.95 (5H, m), 2.10–2.60 (4H, m), 3.09–3.30 (1H, m), 3.58–4.60 (15H, m), 4.69–5.20 (10H, m), 5.24 (1H, d, J=4.5 Hz), 5.51 (1H, d, J=6.0 Hz), 6.68–6.95 (4H, m), 7.04 (1H, d, J=1.0 Hz), 7.10–7.73 (7H, m), 7.73–7.90 (2H, m), 7.98 (1H, d, J=1.9 Hz), 8.10 (1H, d, J=8.4 Hz), 8.32 (1H, d, J=8.4 Hz), 8.50 (1H, d, J=7.7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1275 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{73}N_8O_{22}SNa.5H_2O$: C 50.38, H 6.38, N 8.55 Found: C 49.98, H 6.37, N 8.41

EXAMPLE 22

IR (KBr): 3340, 2931, 1664, 1627, 1531, 1444, 1278, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.6 Hz), 0.96 (3H, d, J=6.8 Hz), 1.08 (3H, d, J=5.9 Hz), 1.2–1.4 (6H, m), 1.5–1.7 (2H, m), 1.7–1.2 (3H, m), 2.2–2.4 (3H, m), 2.6–2.7 (3H, m), 3.1–3.2 (1H, m), 3.7–4.6 (13H, m), 4.78 (1H, d, J=6.0 Hz), 4.8–5.1 (1H, m), 5.09 (1H, d, J=5.6 Hz), 5.16 (1H, d, J=3.2 Hz), 5.24 (1H, d, J=4.4 Hz), 5.52 (1H, d, J=6.0 Hz), 6.73 (1H, d, J=8.2 Hz), 6.83 (2H, d, J=8.3 Hz), 7.05 (1H, s),

7.3–7.5 (5H, m), 7.65 (2H, d, J=8.2 Hz), 7.74 (2H, d, J=8.4 Hz), 7.98 (2H, d, J=8.4 Hz), 8.11 (1H, d, J=8.4 Hz), 8.31 (1H, d, J=8.4 Hz), 8.79 (1H, d, J=7.7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1245 (M^++Na)

Elemental Analysis Calcd. for $C_{54}H_{71}N_8O_{21}SNa.4H_2O$: C 50.07, H 6.15, N 8.65 Found: C 50.26, H 6.44, N 8.67

EXAMPLE 23

NMR (DMSO-d_6, δ): 0.91 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.8 Hz), 1.05 (3H, d, J=5.6 Hz), 1.2–1.5 (6H, m), 1.6–2.1 (5H, m), 2.1–2.7 (4H, m), 3.0–3.5 (9H, m), 3.6–4.5 (15H, m), 4.6–5.6 (11H, m), 6.73 (1H, d, J=8.2 Hz), 6.8–6.9 (4H, m), 6.95 (2H, d, J=8.6 Hz), 7.02 (2H, d, J=9.2 Hz), 7.04 (1H, s), 7.2–7.5 (3H, m), 7.82 (2H, d, J=8.6 Hz), 8.06 (1H, d, J=8 Hz), 8.25 (1H, d, J=6.7 Hz), 8.43 (1H, d, J=6.7 Hz), 8.85 (1H, s)

IR (KBr): 3350, 1668, 1629, 1510 cm^{-1}

FAB-MASS: m/z=1345 (M+Na)

Elemental Analysis Calcd. for $C_{58}H_{79}N_{10}O_{22}SNa.6H_2O$: C 48.67, H 6.41, N 9.78 Found: C 48.80, H 6.46, N 9.82

EXAMPLE 24

Major Product

IR (KBr): 3350, 1668, 1631, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.7 Hz), 1.2–1.6 (10H, m), 1.6–2.4 (8H, m), 2.5–2.7 (1H, m), 3.18 (1H, m), 3.21 (3H, s), 3.29 (2H, t, J=6.4 Hz), 3.6–3.83 (2H, m), 3.83–4.6 (13H, m), 4.7–5.4 (11H, m), 5.51 (1H, d, J=5.9 Hz), 6.73 (1H, d, J=8.2 Hz), 6.83 (1H, d, J=8.2 Hz), 6.85 (1H, s), 7.04 (2H, d, J=8.4 Hz), 7.06 (1H, s), 7.31 (1H, s), 7.2–7.5 (2H, m), 7.67 (2H, d, J=8.4 Hz), 7.71 (2H, d, J=8.4 Hz), 7.96 (2H, d, J=8.4 Hz), 8.06 (1H, d, J=8 Hz), 8.25 (1H, d, J=6.7 Hz), 8.74 (1H, d, J=6.7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1319 (M+Na)

Elemental Analysis Calcd. for $C_{57}H_{77}N_8O_{23}SNa.4H_2O$: C 49.99, H 6.26, N 8.18 Found: C 49.74, H 6.27, N 8.06

Minor Product

IR (KBr): 3350, 1668, 1631 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.7 Hz), 1.2–1.6 (6H, m), 1.6–2.1 (7H, m), 2.1–2.5 (3H, m), 2.5–2.7 (1H, m), 3.18 (1H, m), 3.6–3.8 (2H, m), 3.8–4.6 (13H, m), 4.6–5.2 (12H, m), 5.26 (1H, d, J=4.6 Hz), 5.53 (1H, d, J=5.8 Hz), 5.6–6.0 (1H, m), 6.73 (1H, d, J=8.2 Hz), 6.83 (1H, d, J=8.3 Hz), 6.85 (1H, s), 7.04 (2H, d, J=8.5 Hz), 7.06 (1H, s), 7.30 (1H, s), 7.2–7.5 (2H, m), 7.68 (2H, d, J=8.5 Hz), 7.72 (2H, d, J=8.5 Hz), 7.96 (2H, d, J=8.5 Hz), 8.06 (1H, d, J=8 Hz), 8.25 (1H, d, J=6.7 Hz), 8.74 (1H, d, J=6.7 Hz), 8.85 (1H, s)

FAB-MASS: m/z=1287 (M+Na)

Elemental Analysis Calcd. for $C_{56}H_{73}N_8NaO_{22}S.7H_2O$: C 48.38, H 6.30, N 8.05 Found: C 48.19, H 6.19, N 7.99

Example 25

IR (KBr): 3350, 2935, 2873, 1668, 1629, 1538, 1506, 1438, 1257, 1049 cm^{-1}

NMR (DMSO-d_6, δ): 0.9–1.0 (6H, m), 1.08 (3H, d, J=5.7 Hz), 1.2–1.6 (4H, m), 1.6–2.0 (5H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.2 (1H, m), 3.6–4.6 (15H, m), 4.7–5.2 (10H, m), 5.26 (1H, d J=4.5 Hz), 5.55 (1H, d, J=5.9 Hz), 6.7–6.9 (3H, m), 7.0–7.6 (7H, m), 7.85 (2H, d, J=8.6 Hz), 7.9–8.2 (4H, m), 8.26 (1H, d, J=7.7 Hz), 8.8–9.0 (2H, m)

FAB-MASS: m/z=1314.3 $(M+Na)^+$

Elemental Analysis Calcd. for $C_{56}H_{70}N_9O_{23}NaS.7H_2O$: C 47.42, H 5.97, N 8.89 Found: C 47.33, H 5.85, N 8.73

Example 26

To a solution of The Starting Compound (1 g) and succinimido 4-(4-octyloxyphenyl)piperazine-1-carboxylate (0.45 g) in N,N-dimethylformamide (10 ml) was added 4-dimethylaminopyridine (0.141 g), and stirred for 5 days at 50° C. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration, and dried under reduced pressure. The powder was dissolved in water, and subjected to column chromatography on ion exchange resin (DOWEX-50WX4) eluting with water. The fractions containing the object compound were combined, and subjected to column chromatography on ODS (YMS-gel.ODS-AM.S-50) eluting with 50% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give crude The Object Compound (23). The powder of crude The Object Compound (23) was purified by preparative HPLC utilizing a C_{18}μBondapak resin (Waters Associates, Inc.) which was eluted with a solvent system comprised of (acetonitrile-pH 3 phosphate buffer=40:60) at a flow rate of 80 ml/minute using a Shimadzu LC-8A pump. The column was monitored by a UV detector set at 240 um. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was subjected to column chromatography on ion exchange resin (DOWEX-50WX4) eluting with water. The fractions containing the object compound were combined, and subjected to column chromatography on ODS (YMS-gel.ODS-AM.S-50) eluting with 50% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give The Object Compound (23) (60 mg).

IR (KBr): 3347, 1629, 1511, 1245 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 0.95 (3H, d, J=6.8 Hz), 1.06 (3H, d, J=5.9 Hz), 1.2–1.5 (10H, m), 1.55–1.92 (5H, m), 2.0–2.65 (4H, m), 2.8–3.05 (5H, m), 3.2–4.47 (17H, m), 4.6–5.6 (12H, m), 6.6–7.0 (7H, m), 7.03 (1H, s), 7.2–7.5 (3H, m), 7.9–8.3 (3H, m), 8.84 (1H, s)

FAB-MASS: m/z=1297 (M^++Na)

Elemental Analysis Calcd. For $C_{54}H_{79}N_{10}O_{22}SNa.6H_2O.CH_3CN$: C 47.22, H 6.65, N 10.82 Found: C 47.58, H 7.05, N 10.85

Example 27

To a suspension of 1-hydroxybenzotriazole (0.53 g) and 2-(4-octyloxyphenoxy)acetic acid (1 g) in dichlormethane (30 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide hydrochloride (WSCD.HCl) (0.886 g), and stirred for 3 hours at ambient temperature. The reaction mixture was added to water. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 1-[2-(4-octyloxyphenoxy)actyl] benzotriazole 3-oxide (892 mg). To a solution of The Starting Compound (1.79 g) and 1-[2-(4-octyloxyphenoxy) acetyl]benzotriazole 3-oxide (892 mg) in N,N-dimethylformamide (18 ml) was added 4-(N,N-dimethylamino)pyridine (0.297 g), and stirred for 12 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration, and dried under reduced pressure. The powder was

added to water, and subjected to ion-exchange column chromatography on DOWEX-50WX4, and eluted with water. The fractions containing the object compound were combined, and subjected to column chromatograph on ODS (YMS-gel.ODS-AM.S-50), and eluted with 50% methanol aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove methanol. The residue was lyophilized to give The Object Compound (24) (1.75 g).

IR (KBr): 3350, 1666, 1629, 1228 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.9 Hz), 0.95 (3H, d, J=6.7 Hz), 1.04 (3H, d, J=5.7 Hz), 1.15–1.5 (10H, m), 1.55–2.0 (5H, m), 2.05–2.5 (4H, m), 3.16 (1H, m), 3.72 (2H, m), 3.88 (3H, t, J=6.32 Hz), 4.41 (2H, s), 3.93–4.6 (11H, m), 4.69–5.25 (10H), m), 5.28 (1H, d, J=4.3 Hz), 5.57 (1H, d, J=5.7 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–7.0 (5H, m), 7.04 (1H, s), 7.09 (1H, s), 7.3–7.4 (2H, m), 7.92–8.17 (2H, m), 8.29 (1H, d, J=7.5 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1243 (M^++Na)

Elemental Analysis Calcd. for $C_{51}H_{73}N_8O_{23}SNa.4H_2O$: C 47.36, H 6.31, N 8.66 Found: C 47.22, H 6.44, N 8.37

The Object Compounds (28) to (31) were obtained according to a similar manner to that of Example 27.

Example 28

IR (KBr): 3350, 2933, 1664, 1628, 1446, 1205, 1045 cm^{-1}

NMR (DMSO-d_6, δ): 0.8–1.1 (9H, m), 1.2–2.0 (19H, m), 2.1–2.3 (3H, m), 3.6–3.8 (4H, m), 3.9–4.4 (13H, m), 4.6–5.0 (8H, m), 5.07 (1H, d, J=5.6 Hz), 5.14 (1H, d, J=3.2 Hz), 5.23 (1H, d, J=4.3 Hz), 5.46 (1H, d, J=6.7 Hz), 6.7–6.9 (3H, m), 7.04 (1H, s), 7.2–7.5 (6H, m), 7.8–8.0 (3H, m), 8.05 (1H, d, J=8.4 Hz), 8.2–8.4 (2H, m), 8.83 (1H, s)

FAB-MASS: m/z=1360 (M^++Na)

Elemental Analysis Calcd. for $C_{59}H_{80}N_9O_{23}SNa.6H_2O$: C 48.99, H 6.41, N 8.72 Found: C 48.92, H 6.37, N 8.64

Example 29

IR (KBr): 3350, 2927, 1668, 1627, 1535, 1515, 1452, 1440, 1286, 1045 cm^{-1}

NMR (DMSO-d_6, δ): 0.83 (3H, t, J=6.7 Hz), 0.95 (3H, d, J=6.7 Hz), 1.07 (3H, d, J=5.9 Hz), 1.2–1.4 (12H, m), 1.6–2.0 (5H, m), 2.1–2.4 (3H, m), 2.6 (1H, m), 2.82 (2H, t, J=7.4 Hz), 3.1–3.2 (1H, m), 3.6–4.5 (13H, m), 4.7–5.2 (11H, m), 5.4–5.6 (1H, m), 6.72 (1H, d, J=8.2 Hz), 6.82 (2H, d, J=8.1 Hz), 7.03 (1H, s), 7.2–7.4 (3H, m), 7.47 (1H, d, J=8.5 Hz), 7.69 (1H, d, J=8.5 Hz), 8.1–8.2 (2H, m), 8.23 (1H, d, J=8.4 Hz), 8.62 (1H, d, J=7.8 Hz), 8.83 (1H, s)

FAB-MASS: m/z=1251 (M^++Na)

Elemental Analysis Calcd. for $C_{52}H_{73}N_{10}O_{21}SNa.5H_2O$: C 47.34, H 6.34, N 10.61 Found: C 47.30, H 6.45, N 10.45

Example 30

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.8 Hz), 0.96 (3H, t, J=6.7 Hz), 1.05 (3H, t, J=5.8 Hz), 1.2–1.5 (10H, m), 1.6–2.0 (5H, m), 2.2–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.2 (1H, m), 3.7–4.5 (15H, m), 4.7–4.9 (8H, m), 5.10 (1H, d, J=5.6 Hz), 5.17 (1H, d, J=3.1 Hz), 5.26 (1H, d, J=4.5 Hz), 5.52 (1H, d, J=5.8 Hz) 6.73 (1H, d, J=8.2 Hz), 6.8–7.0 (3H, m), 7.04 (1H, s), 7.2–7.4 (3H, m), 8.0–8.3 (3H, m), 8.68 (1H, d, J=2.3 Hz), 8.7–8.8 (1H, m), 8.85 (1H, m)

FAB-MASS: m/z=1214 (M^++Na)

Elemental Analysis Calcd. for $C_{49}H_{70}N_9O_{22}SNa.4H_2O$: C 46.55, H 6.22, N 9.97 Found: C 46.29, H 6.18, N 9.71

Example 31

IR (Nujol): 3342, 2210, 1668, 1623 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.7 Hz), 0.97 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=6.7 Hz), 1.20–1.60 (8H, m), 1.60–2.00 (5H, m), 2.05–2.50 (4H, m), 3.05–3.30 (1H, m), 3.60–4.60 (15H, m), 4.65–5.18 (10H, m), 5.24 (1H, d, J=4.5 Hz), 5.58 (1H, d, J=6.0 Hz), 6.68–7.10 (4H, m), 7.15–7.65 (5H, m), 7.80–8.30 (6H, m), 8.84 (1H, s), 9.18 (1H, d, J=7.7 Hz)

FAB-MASS: m/z=1273.5 (M^++Na)

Example 32

To a solution of 6-heptyloxy-2-naphthoic acid (0.358 g) and triethylamine (0.174 ml) in N,N-dimethylformamide (10 ml) was added diphenylphosphoryl azide (0.4 ml), and stirred for an hour at ambient temperature. Then, the reaction mixture was stirred for an hour at 100° C. After cooling, to the reaction mixture was added The Starting Compound (1 g) and 4-(N,N-dimethylamino)pyridine (0.140 g), and stirred for 10 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration, and dried under reduced pressure. The powder was dissolved in water, and subjected to column chromatography on ion exchange resin (DOWEX-50WX4) eluting with water. The fractions containing the object compound were combined, and subjected to column chromatography on ODS (YMS-gel.ODS-AM.S-50) eluting with 50% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give The Object Compound (29) (0.832 g).

IR (KBr): 3350, 1664, 1629, 1547, 1240 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.6 Hz), 0.97 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.9 Hz), 1.2–1.55 (8H, m), 1.55–2.0 (5H, m), 2.1–2.5 (4H, m), 3.18 (1H, m), 3.6–3.8 (3H, m), 3.9–4.5 (13H, m), 4.7–4.95 (3H, m), 5.0–5.3 (7H, m), 5.59 (1H, d, J=5.8 Hz), 6.52 (1H, d, J=8.1 Hz), 6.73 (1H, d, J=8.2 Hz), 6.83 (1H, d, J=8.2 Hz), 6.90 (1H, s), 7.0–7.15 (3H, m), 7.20 (1H, s), 7.27–7.4 (3H, m), 7.6–7.7 (2H, m), 7.87 (1H, s), 7.95–8.2 (2H, m), 8.69 (1H, s), 8.85 (1H, s)

FAB-MS: m/z=1264 (M^++Na)

Elemental Analysis Calcd. for $C_{53}H_{72}N_9O_{22}SNa.5H_2O$: C 47.78, H 6.20, N 9.46 Found: C 47.65, H 6.42, N 9.34

The Object Compound (33) was obtained according to a similar manner to that of Example 32.

Example 33

IR (KBr): 3350, 1666, 1629, 1537, 1240 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.7 Hz), 0.97 (3H, d, J=6.7 Hz), 1.09 (3H, d, J=5.8 Hz), 1.2–1.55 (8H, m), 1.55–2.0 (5H, m), 2.07–2.6 (4H, m), 3.18 (1H, m), 3.6–3.85 (3H, m), 3.9–4.5 (13H, m), 4.7–4.98 (3H, m), 5.0–5.3 (7H, m), 5.57 (1H, d, J=8.2 Hz), 6.82 (1H, dd, J=8.2 and 1.7 Hz), 6.87 (1H, s), 6.97 (2H, d, J=8.8 Hz), 7.05 (1H, d, J=1.7 Hz), 7.10 (1H, s), 7.23–7.43 (2H, m), 7.38 (2H, d, J=8.8 Hz), 7.50 (2H, d, J=8.8 Hz), 7.52 (2H, d, J=8.8 Hz), 8.0–8.15 (2H, m), 8.65 (1H, s), 8.84 (1H, s)

FAB-MASS: m/z=1290 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{74}N_9O_{22}SNa.7H_2O$: C 47.38, H 6.36, N 9.04 Found: C 47.67, H 6.53, N 9.03

Example 34

A solution of The Starting Compound (2.45 g), 3-[4-(4-pentylphenyl)phenyl]propiolic acid (0.90 g), 1-ethyl-3-(3'-

dimethylaminopropyl)carbodiimide hydrochloride (WSCD-HCl) (0.59 g) and triethylamine (0.43 ml) in N,N-dimethylformamide (50 ml) was stirred for 15 hours at ambient temperature. The reaction mixture was diluted with ethyl acetate, and the resultant precipitate was collected by filtration, and washed in turn with ethyl acetate and diisopropyl ether, and dried under reduced pressure. The powder was dissolved in water, and was subjected to column chromatography on ion exchange resin (DOWEX-50WX4 (Na form, 50 ml)) eluting with water. The fractions containing the object compound were combined, and subjected to reversed phase chromatography on ODS (YMS-gel-ODS-AM.S-50, 50 ml) eluting with (water:acetonitrile=10:0–7:3, V/V). The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give The Object Compound (31) (1.53 g).

IR (Nujol): 3351, 2212, 1668, 1627 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.5 Hz), 0.96 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.8 Hz), 1.20–1.50 (4H, m), 1.50–2.00 (5H, m), 2.03–2.55 (4H, m), 2.62 (2H, t, J=7.5 Hz), 3.17 (1H, t, J=8.4 Hz), 3.55–4.57 (15H, m), 4.65–5.13 (9H, m), 5.16 (1H, d, J=3.2 Hz), 5.24 (1H, d, J=4.5 Hz), 5.58 (1H, d, J=5.8 Hz), 6.67–6.90 (3H, m), 6.93–7.10 (2H, m), 7.14–7.50 (4H, m), 7.50–7.90 (6H, m), 8.06 (1H, d, J=8.4 Hz), 8.15 (1H, d, J=7.7 Hz), 8.84 (1H, s), 9.19 (1H, d, J=7.1 Hz)

FAB-MASS: m/z=1255 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{69}N_8O_{21}SNa.4H_2O$: C 50.61, H 5.95, N 8.58 Found: C 50.47, H 6.00, N 8.54

Example 35

To a suspension of 1-hydroxybenzotriazole (501 mg) and 4-(4-heptylphenyl)benzoic acid (1 g) in dichloromethane (30 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide hydrochloride (WSCD.HCl) (839 mg), and stirred for 3 hours at ambient temperature. The reaction mixture was added to water. The organic layer was separated, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 1-[4-(4-heptylphenyl) benzoyl]benzotriazole 3-oxide. To a solution of The Starting Compound (2.49 g) and 1-[4-(4-heptylphenyl)benzoyl] benzotriazole 3-oxide in N,N-dimethylformamide (25 ml) was added 4-(N,N-dimethylamino)pyridine (381 mg), and stirred for 12 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration, and dried under reduced pressure. The residue was dissolved in water, and subjected to column chromatography on ion exchange resin (DOWEX-50WX4) eluting with water. The fraction containing the object compound were combined, and subjected to column chromatography on ODS (YMS-gel.ODS-AM-S-50) eluting with 30% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give The Object Compound (32) (1.99 g).

IR (Nujol): 3350, 2852, 1749, 1621, 1457, 1376, 1045 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.9 Hz), 1.5–1.7 (2H, m), 1.7–2.2 (3H, m), 2.2–2.5 (3H, m), 2.6–2.8 (3H, m), 3.1–3.2 (1H, m), 3.7–4.6 (13H, m), 4.7–5.2 (8H, m), 5.12 (1H, d, J=5.5 Hz), 5.18 (1H, d, J=2.9 Hz), 5.27 (1H, d, J=4.4 Hz), 5.54 (1H, d, J=5.8 Hz), 6.7–6.9 (3H, m), 7.05 (1H, s), 7.2–7.4 (5H, m), 7.65 (2H, d, J=8.0 Hz), 7.74 (2H, d, J=8.3 Hz), 7.98 (2H, d, J=8.3 Hz), 8.11 (1H, d, J=8.7 Hz), 8.28 (1H, d, J=8.4 Hz), 8.78 (1H, d, J=7.3 Hz), 8.85 (1H, s)

FAB-MASS: m/z=1259 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{73}N_8O_{21}SNa.5H_2O$: C 49.77, H 6.30, N 8.44 Found: C 49.88, H 6.44, N 8.41

The Object Compounds (36) to (107) were obtained according to a similar manner to that of Example 1.

Example 36

IR (KBr): 3350, 1675.8, 1629.6, 1515.8 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (6H, d, J=6.6 Hz), 0.96 (3H, d, J=6.6 Hz), 1.06 (3H, d, J=5.7 Hz), 1.1–1.3 (2H, m), 1.4–2.0 (6H, m), 2.0–2.7 (4H, m), 3.1–3.5 (9H, m), 3.66 (2H, t, J=7.3 Hz), 3.6–4.5 (13H, m), 4.7–5.6 (12H, m), 6.73 (1H, d, J=8.3 Hz), 6.82 (1H, d, J=8.3 Hz), 6.8–6.9 (1H, m), 7.02 (2H, d, J=9.0 Hz), 7.04 (1H, s), 7.11 (2H, d, J=9.0 Hz), 7.2–7.6 (3H, m), 7.50 (2H, d, J=9.0 Hz), 7.82 (2H, d, J=9.0 Hz), 8.1 (1H, d, J=8.5 Hz), 8.28 (1H, d, J=8.5 Hz), 8.33 (1H, s), 8.45 (1H, d, J=7.0 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1412 (M+Na)

Elemental Analysis Calcd. for $C_{60}H_{80}N_{13}O_{22}SNa.9H_2O$: C 46.42, H 6.36, N 11.73 Found: C 46.64, H 6.43, N 11.62

Example 37

IR (KBr): 3350, 1668.1, 1629.6, 1268.9 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.6 Hz), 0.96 (3H, d, J=6.7 Hz), 1.07 (3H, d, J=5.9 Hz), 1.2–1.4 (10H, m), 1.4–20 (5, m), 2.0–2.5 (4H, m), 2.61 (2H, t, J=7.2 Hz), 3.1–3.3 (1H, m), 3.6–4.5 (13H, m), 4.40 (2H, s), 4.6–5.3 (11H, m), 5.60 (1H, d, J=5.8 Hz), 6.73 (1H, d, J=8.2 Hz), 6.82 (1H, d, J=8.2 Hz), 6.6– 6.9 (1H, m), 7.04 (1H, s), 7.0–7.1 (1H, m), 7.32 (2H, d, J=8.5 Hz), 7.2–7.5 (2H, m), 7.58 (2H, d, J=8.5 Hz), 7.93 (1H, d, J=7 Hz), 8.04 (1H, d, J=9.4 Hz), 8.41 (1H, s), 8.44 (1H, d, J=9.4 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1294 (M+Na)

Elemental Analysis Calcd. for $C_{43}H_{74}N_{11}O_{22}SNa.7H_2O$: C 45.52, H 6.34, N 11.02 Found: C 45.47, H 6.27, N 10.93

Example 38

Major product

IR (KBr): 3349.7, 1670.1, 1627.6, 1508.1 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.6 Hz), 1.06 (3H, d, J=5.7 Hz), 1.2–1.6 (8H, m), 1.6–2.1 (5H, m), 2.1–2.7 (4H, m), 3.0–3.2 (5H, m), 3.21 (3H, s), 3.30 (2H, t, J=6.5 Hz), 3.3–3.5 (4H, m), 3.6–4.5 (15H, m), 4.7–5.3 (11H, m), 5.49 (1H, d, J=5.9 Hz), 6.73 (1H, d, J=8.3 Hz), 6.8–6.9 (4H, m), 6.95 (2H, d, J=9.2 Hz), 7.01 (2H, d, J=8.5 Hz), 7.04 (1H, s), 7.20 (1H, s), 7.2–7.5 (2H, m), 7.81 (2H, d, J=8.5 Hz), 8.09 (1H, d, J=8.7 Hz), 8.28 (1H, d, J=8.7 Hz), 8.45 (1H, d, J=6.7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1389 (M+Na)

Elemental Analysis Calcd. for $C_{60}H_{83}N_{10}O_{23}SNa.8H_2O$: C 47.68, H 6.60, N 9.27 Found: C 47.83, H 6.72, N 9.27

Minor product

IR (KBR: 3338.2, 1646.9, 1511.9 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7 Hz), 1.06 (3H, d, J=5.7 Hz), 1.3–1.6 (4H, m), 1.6–2.7 (11H, m), 3.0–3.2 (5H, m), 3.3–3.5 (4H, m), 3.6–4.5 (15H, m), 4.7–5.3 (13H, m), 5.48 (1H, d, J=5.9 Hz), 5.7–6.0 (1H, m), 6.73 (1H, d, J=8.2 Hz), 6.8–6.9 (4H, m), 6.94 (2H, d, J=9.3Hz), 7.01 (2H, d, J=8.6Hz), 7.04 (1H, s), 7.2–7.5 (3H, m), 7.81 (2H, d, J=8.6Hz), 8.06 (1H, d, J=8.7Hz), 8.25 (1H, d, J=8.7Hz), 8.42 (1H, d, J=6.7Hz), 8.84 (1H, s)

FAB-MASS: m/z=1357 (M+Na)

Elemental Analysis Calcd. For $C_{59}H_{79}N_{10}O_{22}SNa \cdot 9H_2O$: C 47.32, H 6.53, N 9.35 Found: C 47.08, H 6.66, N 9.25

Example 39

IR (KBr): 3350, 1670.1, 1631.5, 1510.0, 1234.2 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.7Hz), 0.96 (3H, d, J=6.7Hz), 1.06 (3H, d, J=5.6Hz), 1.2–1.5 (8H, m), 1.6–2.1 (5H, m), 2.1–2.7 (4H, m), 3.0–3.3 (5H, m), 3.3–3.5 (4H, m), 3.6–3.8 (2H, m), 3.88 (2H, d, J=6.4Hz), 3.8–4.5 (11H, m), 4.7–5.1 (8H, m), 5.10 (1H, d, J=5.6Hz), 5.16 (1H, d, J=3.1Hz), 5.25 (1H, d, J=4.5Hz), 5.48 (1H, d, J=5.9Hz), 6.73 (1H, d, J=8.2Hz), 6.8–6.9 (4H, m), 6.94 (2H, d, J=9.3Hz), 7.01 (2H, d, J=8.7Hz), 7.04 (1H, s), 7.2–7.5 (3H, m), 7.81 (2H, d, J=8.7Hz), 8.06 (1H, d, J=8Hz), 8.25 (1H, d, J=6.7Hz), 8.43 (1H, d, J=6.7Hz), 8.85 (1H, s)

FAB-MASS: m/z=1359 (M+Na)

Elemental Analysis Calcd. for $C_{59}H_{81}N_{10}O_{22}SNa \cdot 5H_2O$: C 49.64, H6.43, N 9.81 Found: C 49.49, H 6.54, N 9.72

Example 40

IR (KBr): 3355.5, 1670.1, 1627.6, 1510.0, 1236.1 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (6H, d, J=6.5Hz), 0.96 (3H, d, J=6.7Hz), 1.05 (3H, d, J=5.7Hz), 1.2–1.4 (2H, m), 1.5–2.1 (6H, m), 2.1–2.7 (4H, m), 3.0–3.6 (9H, m), 3.6–4.5 (15H, m), 4.5–5.4 (12H, m), 6.73 (1H, d, J=8.2Hz), 6.8–6.9 (4H, m), 6.96 (2H, d, J=9.6Hz), 7.02 (2H, d, J=8.7Hz), 7.05 (1H, s), 7.2–7.5 (3H, m), 7.82 (2H, d, J=8.7Hz), 8.08 (1H, d, J=8Hz), 8.27 (1H, d, J=6.7Hz), 8.46 (1H, d, J=6.7Hz), 8.85 (1H, s)

FAB-MASS: m/z=1345 (M+Na)

Elemental Analysis Calcd. for $C_{58}H_{79}N_{10}O_{22}SnA \cdot 8H_2O$: C 47.47, H 6.52, N 9.54 Found: C 47.47, H 6.54, N 9.51

Example 41

IR (KBr): 3347.8, 1668.1, 1629.6, 1510.0, 1234.2 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (3H, t, J=7.0Hz), 0.96 (3H, d, J=6.7Hz), 1.05 (3H, d, J=5.8Hz), 1.2–1.5 (4H, m), 1.6–2.1 (5H, m), 2.1–2.7 (4H, m), 3.0–3.6 (9H, m), 3.6–3.8 (2H, m), 3.8–4.5 (13H, m), 4.7–5.6 (12H, m), 6.73 (1H, d, J=8.2Hz), 6.8–6.9 (4H, m), 6.96 (2H, d, J=8.7Hz), 7.02 (2H, d, J=9.0Hz), 7.04 (1H, s), 7.2–7.5 (3H, m), 7.82 (2H, d, J=8.7Hz), 8.07 (1H, d, J=8Hz), 8.27 (1H, d, J=6.7Hz), 8.45 (1H, d, J=6.7Hz), 8.85 (1H, s)

FAB-MASS: m/z=1331 (M+Na)

Elemental Analysis Calcd. for $C_{57}H_{77}N_{10}O_{22}SNa \cdot 6H_2O$: C 48.30, H 6.33, N 9.88 Found: C 48.20, H 6.58, N10.03

Example 42

Mixture product

IR (KBr): 3344, 1670.1, 1631.5 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7Hz), 1.08 (3H, d, J=5.9Hz), 1.2–1.5 (8H, m), 1.6–2.1 (7H, m), 2.1–2.7 (4H, m), 3.1–3.3 (1H, m), 3.6–4.5 (15H, m) 4.45 and 4.70 (2H, t, J=7.1Hz), 4.6–5.3 (11H, m), 5.52 (1H, d, J=5.9Hz), 6.73 (1H, d, J=8.2Hz), 6.83 (1H, d, J=8.2Hz), 6.85 (1H, s), 7.03 (2H, d, J=8.6Hz), 7.05 (1H, s), 7.2–7.5 (3H, m), 7.68 (2H, d, J=8.6Hz), 7.71 (2H, d, J=8.4Hz), 7.96 (2H, d, J=8.4Hz), 8.12 (1H, d, J=8.5Hz), 8.30 (1H, d, J=7.0Hz)

FAB-MASS: m/z=1357 (M+Na)

Elemental Analysis Calcd. for $C_{57}H_{75}N_{12}O_{22}Sna \cdot 4H_2O$: C 48.64, H 5.94, N 11.94 Found: C 48.91, H 5.88, N 11.86

Example 43

IR (KBr): 3350, 1666.2, 1651.5 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7Hz), 1.05 (6H, d, J=6.3Hz), 1.06 (3H, d, J=5.7Hz), 1.2–1.6 (10H, m), 1.6–2.1 (7H, m), 2.1–2.7 (6H, m), 2.8–3.0 (2H, m), 3.9–3.2 (1H, m), 3.4–3.7 (2H, m, 3.6–3.8 (2H, m), 3.8–4.5 (13H, m), 4.7–5.6 (12H, m), 6.73 (1H, d, J=8.2Hz), 6.8–7.0 (2H, m), 7.03 (2H, d, J=8.7Hz), 7.06 (1H, s), 7.2–7.5 (3H, m), 7.67 (2H, d, J=8.7Hz), 7.71 (2H, d, J=8.4Hz), 7.96 (2H, d, J=8.4Hz), 8.04 (1H, d, J=8.5Hz), 8.31 (1H, d, J=8.5Hz), 8.73 (1H, d, J=7.0Hz), 8.90 (1H, s)

FAB-MASS: m/z=1402 (M+Na)

Example 44

IR (KBr pelet): 3350, 2929, 2856, 1670, 1631, 1510, 1243, 1045 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.8Hz), 0.96 (3H, d, J=6.7Hz), 1.06 (3H, d, J=5.7Hz), 1.6–2.0 (5H, m), 2.2–2.5 (5H, m), 2.6–2.7 (1H, m), 3.0–3.3 (5H, m), 3.6–4.5 (19H, m), 4.77 (2H, d, J=5.9Hz), 4.8–5.1 (6H, m), 5.10 (1H, d, J=4.5Hz), 5.50 (1H, d, J=3.1H), 5.25 (1H, d, J=4.5Hz), 5.50 (1H, d, J=5.8Hz), 6.7–7.0 (8H, m), 7.04 (1H, s), 7.2–7.4 (3H, m), 8.0–8.2 (2H, m), 8.26 (1H, d, J=8.0Hz), 8.55 (1H, d, J=7.3Hz), 8.67 (1H, d, J=1.2Hz), 8.85 (1H, s)

FAB-MASS: m/z=1374.3 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{59}H_{82}N_{11}O_{22}NaS \cdot 5.5H_2O$: C 48.82, H 6.46, N 10.61 Found: C 48.89, H 6.74, N 10.50

Example 45

IR (KBr): 3350, 2935, 1668, 1623, 1538, 1257, 1174, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.8–1.1 (6H, m), 1.09 (3H, d, J=5.7Hz), 1.2–1.6 (6H, m), 1.7–2.1 (5H, m), 2.2–2.4 (3H, m), 2.5–2.6 (1H, m), 3.6–3.8 (2H, m), 3.8–4.6 (14H, m), 4.8–5.2 (7H, m), 5.18 (1H, d, J=3.1Hz), 5.26 (1H, d, J=4.5Hz), 5.54 (1H, d, J=5.8Hz), 6.7–7.5 (9H, m), 7.82 (1H, d, J=8.5Hz), 7.96 (1H, d, J=8.7Hz), 8.1–8.4 (5H, m), 8.8–9.0 (2H, m)

FAB-MASS: m/z=1302.6 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{55}H_{70}N_9O_{23}SNa \cdot 6H_2O$: C 47.58, H 5.95, N 9.08 Found: C 47.46, H 6.04, N 9.05

Example 46

IR (KBr): 3355, 2958, 1670, 1627, 1521, 1247, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.9–1.0 (6H, m), 1.08 (3H, d, J=5.6Hz), 1.4–1.6 (2H, m), 1.7–2.1 (5H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.3 (1H, m), 3.7–3.8 (2H, m), 3.9–4.6 (13H, m), 4.8–5.1 (8H, m), 5.11 (1H, d, J=5.6Hz), 5.17 (1H, d, J=3.1Hz), 5.26 (1H, d, J=4.5Hz), 5.54 (1H, d, J=5.9Hz), 6.7–6.9 (3H, m), 7.0–7.2 (3H, m), 7.3–7.5 (3H, m), 7.7–7.9 (8H, m), 8.02 (2H, d, J=8.4Hz), 8.08 (1H, d, J=8.4Hz), 8.32 (1H, d, J=7.7Hz), 8.81 (1H, d, J=7.0Hz), 8.85 (1H, s)

FAB-MASS: m/z=1309.3 $(M+Na)^+$

Elemental Analysis Calcd. for $C_{58}H_{71}N_8O_{22}NaS \cdot 6H_2O$: C 49.92, H 6.00, N 8.03 Found: C 49.92, H 5.97, N 8.03

Example 47

IR (KBr): 3350, 2933, 1668, 1629, 1517, 1249, 1045 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.7Hz), 0.96 (3H, d, J=6.7Hz), 1.08 (3H, d, J=5.8Hz), 1.7–2.7 (8H, m), 3.1–3.3 (1H, m), 3.6–4.5 (16H, m), 4.7–5.2 (8H, m), 5,18 (1H, d, J=3.1Hz), 5.27 (1H, d, J=4.5Hz), 5.56 (1H, d, J=5.8Hz), 6.7–7.0 (3H, m), 7.0–7.2 (3H, m), 7.2–7.5 (3H, m), 8.0–8.4 (6H, m), 8.85 (1H, s), 8.96 (1H, d, J=7.0Hz), 9.07 (1H, s)

FAB-MASS: m/z=1276.6 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{54}H_{72}N_9O_{22}NaS \cdot 5H_2O$: C 48.25, H 6.15, N 9.38 Found: C 48.10, H 6.14, N 9.30

Example 48

IR (KBr): 3350, 2931, 1668, 1629, 1537, 1049 cm^{-1}

NMR (DSMO-d_6, δ): 0.86 (3H, t, J=6.9Hz), 0.9–1.5 (16H, m), 1.6–2.4 (8H, m), 2.5–2.7 (1H, m), 3.1–3.3 (1H, m), 3.5–5.6 (25H, m), 6.6–7.4 (8H, m), 7.8–8.4 (6H), 8.7–9.0 (2H, m), 9.00 (1H, d, J=2.4Hz)

FAB-MASS: m/z=1331.4 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{56}H_{73}N_{10}O_{23}NaS \cdot 8H_2O$: C 46.28, H 6.17, N 9.64 Found: C 46.50, H, 6.27, N 9.65

Example 49

IR (KBr pelet): 3300, 2931, 1668, 1650, 1629, 1538, 1515, 1268, 1049 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.6Hz), 0.97 (3H, d, J=.7Hz), 1.10 (3H, d, J=5.6Hz), 1.2–1.4 (6H, m), 1.5–1.7 (2H, m), 1.7–2.1 (3H, m), 2.1–2.4 (3H, m), 2.6–2.7 (3H, m), 3.1–3.2 (1H, m), 3.7–3.9 (2H, m), 3.9–4.5 (12H, m), 4.8–5.1 (7H, m), 5.11 (1H, d, J=5.5Hz), 5.18 (1H, d, J=3.1Hz,), 5.27 (1H, d, J=4.5Hz), 5.55 (1H, d, J=5.8Hz), 6.7–7.0 (3H, m), 7.06 (1H, s), 7.3–7.5 (5H, m), 7.72 (2H, d, J=8.2Hz), 7.9–8.2 (5H, m), 8.3–8.4 (4H, m), 8.9–9.0 (2H, m)

FAB-MASS: m/z=1260.5 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{61}H_{74}N_9O_2SNa \cdot 6H_2O$: C 50.58, H 5.98, N 8.70 Found: C 50.34, H 6.16, N 8.55

Example 50

IR (KBr): 3369, 2958, 2935, 1670, 1629, 1525, 1473, 1247, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.95 (3H, t, J=7.3Hz), 0.97 (3H, d, J=6.7Hz), 1.09 (3H, d, J=5.7Hz), 1.3–1.6 (2H, m), 1.7–2.1 (5H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.3 (1H, m), 3.7–4.6 (15H, m), 4.7–5.1 (8H, m), 5.10 (1H, d, J=5.6Hz), 5.18 (1H, d, J=3.1Hz), 5.26 (1H, d, J=4.4Hz), 5.56 (1H, d, J=5.7Hz), 6.7–7.0 (3H, m), 7.1–7.2 (3H, m), 7.2–7.4 (3H, m), 7.70 (2H, d, J=8.6Hz), 7.78 (2H, d, J=8.4Hz), 8.1–8.4 (6H, m), 8.85 (1H, s), 8.99 (1H, d, J=7.0Hz), 9.13 (1H, d, J=1.6Hz)

FAB-MASS: m/z=1310.01 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{57}H_{70}N_9O_{22}NaS \cdot 7H_2O$: C 47.20, H 6.12, N 8.69 Found: C 47.42, H 6.19, N 8.92

Example 51

IR (KBr): 3351, 2937, 2875, 1670, 1627, 1533, 1245, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7Hz), 1.08 (3H, d, J=5.7Hz), 1.5–1.7 (2H, m), 1.7–2.1 (7H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.2 (1H, m), 3.7– 3.8 (2H, m), 3.9–4.6 (15H, m), 4.7–4.9 (3H, m), 5.0–5.1 (5H, m), 5.10 (1H, d, J=5.6Hz), 5.17 (1H, d, J=3.1Hz), 5.26 (1H, d, J=4.5Hz), 5.52 (1H, d, J=5.9Hz), 6.7–7.1 (9H, m), 7.2–7.5 (5H, m), 7.68 (2H, d, J=8.2Hz), 7.72 (2H, d, J=6.7Hz), 7.96 (2H, d, J=8.2Hz), 8.06 (1H, d, J=8.4Hz), 8.28 (1H, d, J=7.7Hz), 8.76 (1H, d, J=7.0Hz), 8.85 (1H, s)

FAB-MASS: m/z=1339.5 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{59}H_{73}N_8O_{23}NaS \cdot 7H_2O$: C 49.09, H 6.08, N 7.76 Found: C 49.04, H 6.08, N 7.82

Example 52

IR (KBr): 3350, 2954, 2937, 1670, 1631, 1440, 1257, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (3H, t, J=6.8Hz), 0.97 (3H, d, J=6.7Hz), 1.09 (2H, d, J=5.8Hz), 1.2–1.5 (6H, m), 1.7–2.1 (5H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.2 (1H, m), 3.7–4.6 (15H, m), 4.75–5.3 (11H, m), 5.5–5.6 (1H, m), 6.7–6.9 (1H, m), 7.0–7.5 (6H, m), 8.0–8.4 (8H, m), 8.85 (1H, s), 8.96 (1H, d, J632 7.0Hz)

APCI-MASS: m/z=1329.0 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{56}H_{71}N_{10}O_{23}NaS \cdot 6H_2O$: C 47.52, H 5.91, N 9.90 Found: C 47.42, H 6.05, N 9.90

Example 53

IR (KBr): 3350, 2952, 1666, 1629, 1537, 1519, 1255 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (3H, t, J=6.7Hz), 0.96 (3H, d, J=6.4Hz), 1.08 (3H, d, J=5.6Hz), 1.7–2.4 (8H, m), 2.5–2.6 (1H, m), 3.7–4.5 (15H, m), 4.7–5.1 (8H, m), 5.11 (1H, d, J=5.5Hz), 5.17 (1H, d, J=3.1Hz), 5.26 (1H, d, J=3.1Hz), 5.56 (1H, d, J=5.7Hz), 6.73 (1H, d, J=8.2Hz), 6.7–7.0 (2H, m), 7.05 (1H, s), 7.13 (2H, d, J=8.7Hz), 7.2–7.5 (3H, m), 7.97 (2H, d, J=8.7Hz), 8.1–8.4 (6H, m), 8.85 (1H, s), 8.92 (1H, d, J=7.0Hz)

FAB-MASS: m/z=1345.3 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{56}H_{71}N_{10}O_{22}S_2Na \cdot 8H_2O$: C 45.84, H 5.98, H 9.55 Found: C 45.87, H 6.07, N 9.55

Example 54

IR (KBr pelet): 3350, 2931, 1670, 1652, 1628, 1442, 1247, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.6Hz), 0.97 (3H, d, J=6.8Hz), 1.12 (3H, d, J=6.8Hz), 1.2–1.5 (10H, m), 1.7–2.0 (5H, m), 2.2–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.2 (1H, m), 3.72 (2H, br), 3.8–4.5 (17H, m), 4.7–5.2 (9H, m), 5.26 (1H, d, J=4.6Hz), 5.57 (1H, d, J=5.7Hz), 6.7–7.1 (7H, m), 7.3–7.5 (3H, m), 7.66 (2H, d, J=8.7Hz), 8.10 (1H, d, J=7.6Hz), 8.17 (1H, d, J=7.6Hz), 8.76 (1H, d, J=7.0Hz), 8.85 (1H, s)

FAB-MASS: m/z=1293 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{54}H_{75}N_{10}O_{22}NaS \cdot 7H_2O$: C 46.41, H 6.42, N 10.02 Found: C 46.51, H 6.43, N 9.95

Example 55

IR (KBr): 3345, 2937, 1650, 1511, 1249, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.91 (3H, t, J=7.0Hz), 0.96 (3H, t, J=7.8Hz), 1.09 (3H, d, J=6.8Hz), 1.3–1.5 (4H, m), 1.6–2.1 (5H, m), 2.1–2.5 (3H, m), 2.5–2.6 (1H, m), 3.1–3.3 (1H, m), 3.7–3.9 (2H, m), 3.9–4.6 (13H, m), 4.79 (2H, d, J=5.9Hz), 4.8–4.9 (1H, m), 4.9–5.2 (5H, m), 5.10 (1H, d, J=5.9Hz), 5.17 (1H, d, J=3.1Hz), 5.25 (1H, d, J=4.6Hz), 5.53 (1H, d, J=5.9Hz), 6.7–7.0 (3H, m), 7.0–7.2 (3H, m), 7.19 (1H, s), 7.3–7.5 (3H, m), 7.7–8.1 (6H, m), 8.08 (1H, d, J=10.0Hz), 8.26 (1H, d, J=8.8Hz), 8.77 (1H, m), 8.85 (1H, s), 13.32 (1H, s)

FAB-MASS: m/z=1314.0 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{56}H_{71}N_{10}O_{22}SNa \cdot 8H_2O$: C 46.86, H 6.11, N 9.76 Found: C 46.93, H 5.87, N 9.74

Example 56

IR (KBr): 3350, 2958, 2935, 2873, 1666, 1629, 1247, 1045 cm^{-1}

NMR (DMSO-d_6, δ): 0.9–1.1 (6H, m), 1.08 (3H, d, J=6.0Hz), 1.4–1.6 (2H, m), 1.6–2.1 (5H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.3 (1H, m), 3.6–4.5 (15H, m), 4.7–5.1 (8H, m), 5.10 (1H, d, J=5.5Hz), 5.17 (1H, d, J=2.9Hz), 5.25 (1H, d, J=4.5Hz), 5.55 (1H, d, J=5.7Hz), 6.7–6.9 (3H, m), 7.0–7.5 (8H, m), 7.68 (2H, d, J=8.9Hz),

7.73 (2H, d, J=8.3Hz), 8.01 (2H, d, J=8.3Hz), 8.10 (1H, d, J=8.4Hz), 8.26 (1H, d, J=7.7Hz), 8.8–9.0 (2H, m)

FAB-MASS: m/z=1299.5 $(M+Na)^+$

Elemental Analysis Calcd. for $C_{56}H_{69}N_8O_{23}NaS \cdot 6H_2O$: C 48.55, H 5.89, N 8.09 Found: C 48.52, H 5.94, N 8.07

Example 57

IR (KBr): 3355.5, 1662.3, 1629.6, 1267.0 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.8Hz), 0.93 (3H, d, J=8.4Hz), 0.97 (3H, d, J=6.7Hz), 1.2–1.5 (4H, m), 1.5–1.95 (5H, m), 2.1–2.45 (4H, m), 2.5–2.7 (4H, m), 3.17 (1H, m), 3.55–4.45 (14H, m), 4.6–5.3 (13H, m), 5.56 (1H, d, J=5.6Hz), 6.72 (1H, d, J=8.1Hz), 6.75 (1H, s), 6.77 (1H, d, J=8.1Hz), 7.04 (1H, s), 7.10 (1H, s), 7.2–7.45 (10H, m), 7.53 (4H, d, J=6.6Hz), 7.85 (1H, d, J=7Hz), 7.92 (1H, d, J=7Hz), 8.05 (1H, d, J=7Hz), 8.22 (1H, d, J=7Hz), 8.84 (1H, s)

FAB-MASS: m/z=1408 (M+Na)

Example 58

IR (KBr): 3347.8, 1664.3, 1631.5, 1245.8 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.6Hz), 0.96 (3H, d, J=6.6Hz), 1.04 (3H, d, J=5.7Hz), 1.15–2.6 (21H, m), 3.16 (1H, m), 3.5–4.5 (16H, m), 4.6–5.4 (13H, m), 5.47 (1H, d, J=5.7Hz), 6.73 (1H, d, J=8.2Hz) 6.78–6.85 (4H, m), 7.05 (1H, s), 7.10 (1H, s), 7.18 (2H, d, J=8.6Hz), 7.25–7.45 (6H, m), 7.72 (1H, d, J=7Hz), 7.91 (1H, d, J=7Hz), 8.05 (1H, d, J=9.3Hz), 8.20 (1H, d, J=7Hz), 8.85 (1H, s)

FAB-MASS: m/z=1390 (M+Na)

Elemental Analysis Calcd. for $C_{60}H_{82}N_9O_{24}SNa \cdot 5H_2O$: C 49.41, H 6.36, N 8.64 Found: C 49.77, H 6.71, N 8.71

Example 59

IR (KBr): 3353.6, 1670.1, 1627.6, 1247.7 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.5Hz), 0.97 (3H, d, J=6.8Hz), 1.01 (3H, d, J=5.4Hz), 1.1–1.55 (12H, m), 1.55–1.95 (5H, m), 2.05–4.7 (4H, m), 3.16 (1H, m), 3.5–4.5 (16H, m), 4.6–5.3 (13H, m), 5.55 (1H, d, J=5.6Hz), 6.7–6.9 (5H, m), 7.05 (1H, s), 7.1 (1H, s), 7.15 (1H, d, J=8.5Hz), 7.25–7.5 (6H, m), 7.73 (1H, d, J=8.4Hz), 7.92 (1H, d, J=7Hz), 8.08 (1H, d, J=8.4Hz), 8.18 (1H, d, J=7Hz), 8.84 (1H, s)

FAB-MASS: m/z=1390 (M+Na)

Example 60

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.6Hz), 0.96 (3H, d, J=6.6Hz), 1.05 (3H, d, J=5.6Hz), 1.1–1.5 (22H, m), 1.5–2.5 (9H, m), 2.5–3.5 (4H, m), 3.5–4.45 (14H, m), 4.45–5.45 (12H, m), 6.72 (1H, d, J=8.2 Hz), 6.79 (1H, s), 6.81 (1H, d, J=8.2 Hz), 7.04 (1H, s), 7.05–7.5 (8H, m), 7.9–8.3 (3H, m), 8.84 (1H, s)

FAB-MASS: m/z=1325 (M+Na)

Elemental Analysis Calcd. for $C_{58}H_{89}N_8O_{22}SNa.6H_2O$: C 49.35, H 7.14, N 7.94 Found: C 49.33, H 7.04, N 7.87

Example 61

IR (KBr): 3400, 1668.1, 1629.6, 1270.9 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.8 Hz), 1.06 (3H, d, J=5.7 Hz), 1.1–2.0 (33H, m), 2.1–2.5 (4H, m), 3.20 (3H, s), 3.28 (2H, t, J=6.5 Hz), 3.1–3.3 (1H, m), 3.6–4.45 (14H, m), 4.6–5.3 (13H, m), 5.49 (1H, d, J=6.1 Hz), 6.70 (1H, s), 6.72 (1H, d, J=8.2 Hz), 6.80 (1H, d, J=8.2 Hz), 7.03 (1H, s), 7.0–7.1 (1H, m), 7.15 (1H, s), 7.2–7.45 (6H, m), 8.0–8.3 (3H, m), 8.83 (1H, s)

FAB-MASS: m/z=1426 (M+Na)

Elemental Analysis Calcd. for $C_{62}H_{94}N_9O_{24}SNa.5H_2O$: C 49.82, H 7.01, N 8.43 Found: C 49.86, H7.31, N 8.40

Example 62

IR (KBr): 3355.5, 1668.1, 1629.6, 1274.7 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.5 Hz), 0.96 (3H, d, J=6.7 Hz), 1.04 (3H, d, J=5.9 Hz), 1.1–2.6 (34H, m), 3.2 (1H, m), 3.6–4.55 (14H, m), 4.7–5.3 (11H, m), 5.47 (1H, d, J=5.9 Hz), 6.72 (1H, d, J=8.1 Hz), 6.79 (1H, s), 6.81 (1H, d, J=8.1 Hz), 7.05 (1H, s), 7.11 (1H, s), 7.2–7.5 (2H, m), 8.0–8.15 (2H, m), 8.20 (1H, d, J=8.0 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1235 (M+Na)

Elemental Analysis Calcd. for $C_{51}H_{81}N_8O_{22}SNa.7H_2O$: C 45.73, H7.15, N 8.37 Found: C 45.55, H 7.24, N 8.23

Example 63

IR (KBr): 3353.6, 1664.3, 1627.6 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.6 Hz), 0.95 (3H, d, J=6.7 Hz), 1.04 (3H, d, J=5.7 Hz), 1.2–2.7 (30H, m), 3.16 (1H, m), 3.6–4.5 (13H, m), 4.7–5.3 (11H, m), 5.51 (1H, d, J=6.0 Hz), 5.74 (1H, s), 6.72 (1H, d, J=8.2 Hz), 6.75 (1H, s), 6.77 (1H, d, J=8.2 Hz), 7.05 (1H, s), 7.2–7.5 (3H, m), 8.0–8.3 (3H, m), 8.85 (1H, s)

FAB-MASS: m/z=1204 (M+Na)

Elemental Analysis Calcd. for $C_{50}H_{77}N_8O_{21}SNa.5H_2O$: C 47.24, H 6.90, N 8.81 Found: C 46.98, H 7.12, N 8.72

Example 64

Major Product

IR (KBr): 3400, 1675.8, 1631.5, 1511.9, 1234.2 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.6 Hz), 1.05 (3H, d, J=5.8 H z), 1.2–1.6 (10H, m), 1.6–2.1 (5H, m), 2.1–2.7 (4H, m), 3.05–3.2 (4H, m), 3.20 (3H, s), 3.29 (2H, t, J=6.4 Hz), 3.3–3.5 (5H, m), 3.6–4.5 (15H, m), 4.7–5.3 (11H, m), 5.50 (1H, d, J=5.8 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–7.1 (9H, m), 7.2–7.5 (3H, m), 7.81 (2H, d, J=8.6 Hz), 8.08 (1H, d, J=8.2 Hz), 8.24 (1H, d, J=7 Hz), 8.44 (1H, d, J=7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1403 (M+Na)

Elemental Analysis Calcd. for $C_{61}H_{85}N_{10}O_{23}Sna.9H_2O$: C 47.47, H 6.73, N 9.07 Found: C 47.43, H 7.06, N 9.03

Minor Product

IR (KBr): 3350, 1668.1, 1631.5, 1511.9, 1234.2 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.6 Hz), 1.07 (3H, d, J=5.8 Hz), 1.2–1.5 (6H, m), 1.55–2.1 (7H, m), 2.1–2.65 (4H, m), 3.0–3.6 (9H, m), 3.7–4.5 (15H, m), 4.7–5.6 (14H, m), 5.7–6.0 (1H, m), 6.72 (1H, d, J=8.0 Hz), 6.75–7.1 (9H, m), 7.25–7.5 (3H, m), 7.81 (2H, d, J=8.3 Hz), 8.08 (1H, d, J=8.2 Hz), 8.25 (1H, d, J=7 Hz), 8.45 (1H, d, J=7 Hz), 8.85 (1H, s)

FAB-MASS: m/z=1371 (M+Na)

Elemental Analysis Calcd. for $C_{60}H_{81}N_{10}O_{22}Sna.8H_2$: C 48.25, H 6.55, N 9.38 Found: C 48.10, H 6.81, N 9.40

Example 65

IR (KBr): 3450, 1668.1, 1635.3 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.5 Hz), 0.96 (3H, d, J=6.7 Hz), 1.06 (3H, d, J=6 Hz), 1.2–1.5 (6H, m), 1.6–2.1 (5H, m), 2.1–2.7 (4H, m), 3.1–3.4 (9H, m), 3.6–4.5 (15H, m), 4.7–5.3 (11H, m), 5.49 (1H, d, J=5.8 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–7.0 (2H, m), 6.83 (2H, d, J=9.0 H z), 6.94

(2H, d, J=9.0 Hz), 7.04 (1H, s), 7.12 (1H, t, J=8.4 Hz), 7.2–7.5 (3H, m), 7.65–7.8 (2H, m), 8.09 (1H, d, J=8.4 Hz), 8.25 (1H, d, J=7 Hz), 8.63 (1H, d, J=7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1363 (M+Na)

Elemental Analysis Calcd. for $C_{58}H_{78}FN_{10}O_{22}SNa.5H_2O$: C 48.67, H 6.20, N 9.79 Found: C 48.83, H 6.15, N 9.74

Example 66

IR (KBr): 3400, 1668.1, 1635.3, 1510.0, 1240.0 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.6 Hz), 1.2–1.5 (6H, m), 1.5–2.05 (5H, m), 2.1–2.65 (4H, m), 3.1–3.3 (9H, m), 3.6–4.5 (15H, m), 4.7–5.3 (11H, m), 5.51 (1H, d, J=5.8 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–6.9 (4H, m), 6.94 (2H, d, J=9.2 Hz), 7.04 (1H, s), 7.24 (1H, d, J=8.5 Hz), 7.15–7.5 (3H, m), 7.86 (1H, dd, J=8.6 and 2.1 Hz), 8.02 (1H, d, J=2.1 Hz), 8.04 (1H, d, J=8.4 Hz), 8.23 (1H, d, J=7 Hz), 8.70 (1H, d, J=7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1379 (M+Na)

Elemental Analysis Calcd. for $C_{58}H_{78}ClN_{10}O_{22}Sna.6H_2O$: C 47.52, H 6.19, N 9.55 Found: C 47.78, H 6.23, N 9.55

Example 67

IR (KBr): 3400, 1670 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7 Hz), 1.05 (3H, d, J=5.7 Hz), 1.4–2.65 (17H, m), 2.65–3.6 (8H, m), 3.6–4.5 (15H, m), 4.6–5.3 (11H, m), 5.44 (1H, d, J=6.0 Hz), 6.73 (1H, d, J=8.2 Hz), 6.81 (1H, s), 6.83 (1H, d, J=8.2 Hz), 6.98 (2H, d, J=8.9 Hz), 7.05 (1H, s), 7.2–7.5 (3H, m), 7.80 (2H, d, J=8.9 Hz), 8.05 (1H, d, J=8.4 Hz), 8.26 (1H, d, J=7 Hz), 8.39 (1H, d, J=7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1229 (M+Na)

Elemental Analysis Calcd. for $C_{52}H_{74}N_{10}O_{21}S.5H_2O$: C 48.14, H 6.53, N 10.80 Found: C 48.29, H 6.33, N 10.95

Example 68

IR (KBr): 3400, 1652.7, 1635.3, 1511.9, 1241.9 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.6 Hz), 0.97 (3H, d, J=6.7 Hz), 1.09 (3H, d, J=5.7 Hz), 1.2–1.5 (6H, m), 1.6–2.0 (5H, m), 2.1–2.6 (4H, m), 3.0–3.3 (5H, m), 3.6–4.6 (19H, m), 4.7–5.3 (11H, m), 5.53 (1H, d, J=5.6 Hz), 6.73 (1H, d, J=8.2 Hz), 6.75–7.0 (2H, m), 6.83 (2H, d, J=9.2 Hz), 6.95 (2H, d, J=9.2 Hz), 7.05 (1H, s), 7.12 (1H, s), 7.25–7.5 (2H, m), 7.42 (1H, d, J=9.5 Hz), 7.84 (1H, d, J=9.5 Hz), 7.9–8.1 (2H, m), 8.71 (1H, d, J=7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1347 (M+Na)

Elemental Analysis Calcd. for $C_{56}H_{77}N_{12}O_{22}SNa.7H_2O$: C 46.34, H 6.32, N 11.58 Found: C 46.38, H 6.18, N 11.36

Example 69

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.6 Hz), 0.97 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.8 Hz), 1.2–1.5 (6H, m), 1.6–2.05 (5H, m), 2.1–2.6 (4H, m), 3.0–3.3 (5H, m), 3.4–3.55 (4H, m), 3.7–4.6 (1.5H, m), 4.7–5.3 (11H, m), 5.52 (1H, d, J=5.8 Hz), 6.73 (1H, d, J=8.1 Hz), 6.8–6.95 (2H, m), 6.83 (2H, d, J=9.3 Hz), 6.95 (2H, d, J=9.3 Hz) 7.05 (1H, s), 7.14 (1H, s), 7.3–7.6 (3H, m), 7.84 (1H, d, J=8.6 Hz), 7.95–8.1 (2H, m), 8.40 (1H, s), 8.42 (1H, d, J=7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1346 (M+Na)

Elemental Analysis Calcd. for $C_{57}H_{78}N_{11}O_{22}SNa.5H_2O$: C 48.40, H 6.27, N 10.89 Found: C 48.32, H 6.44, N 10.86

Example 70

IR (KBr): 3400, 1668.1, 1629.6, 1511.9 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7 Hz), 1.06 (3H, d, J=5.7 Hz), 1.15–1.5 (6H, m), 1.6–2.0 (7H, m), 2.1–2.65 (5H, m), 3.1–3.5 (9H, m), 3.6–4.5 (13H, m), 4.7–5.3 (11H, m), 5.46 (1H, d, J=5.9 Hz), 6.73 (1H, d, J=8.2 Hz), 6.81 (1H, s), 6.84 (1H, d, J=8.2 Hz), 6.91 (2H, d, J=8.7 Hz), 6.95–7.05 (3H, m), 7.09 (2H, d, J=8.7 Hz), 7.25–7.5 (3H, m), 7.81 (2H, d, J=8.8 Hz), 8.09 (1H, d, J=7 Hz), 8.25 (1H, d, J=7 Hz), 8.04 (1H, d, J=7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1327 (M+Na)

Elemental Analysis Calcd. for $C_{58}H_{77}N_{10}O_{21}SNa.5H_2O$: C 49.92, H 6.28, N 10.03 Found: C 49.75, H 6.41, N 10.25

Example 71

IR (KBr): 3350, 1668.1, 1629.6, 1511.9, 1232.3 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.5 Hz), 0.96 (3H, d, J=6.7 Hz), 1.06 (3H, d, J=6.0 Hz), 1.2–1.4 (6H, m), 1.4–1.6 (2H, m), 1.7–2.1 (3H, m), 2.1–2.7 (6H, m), 3.1–3.5 (9H, m), 3.72 (2H, m), 3.8–4.5 (11H, m), 4.7–5.3 (11H, m), 5.47 (1H, d, J=5.9 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–6.9 (2H, m), 6.91 (2H, d, J=8.6 Hz), 6.95–7.15 (5H, m), 7.25–7.5 (3H, m), 7.81 (2H, d, J=8.8 Hz), 8.09 (1H, d, J=8.4 Hz), 8.26 (1H, d, J=7 Hz), 8.40 (1H, d, J=7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1329 (M+Na)

Elemental Analysis Calcd. for $C_{56}H_{79}N_{10}NaO_{21}S.6H_2O$: C 49.22, H 6.48, N 9.90 Found: C 49.33, H 6.67, N 9.89

Example 72

IR (KBr): 3450, 1668.1, 1631.5, 1240.0 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.6 Hz), 1.05 (3H, d, J=5.6 Hz), 1.3–1.7 (4H, m), 1.7–2.1 (7H, m), 2.1–2.73 (6H, m), 2.75–3.05 (4H, m), 3.05–4.5 (18H, m), 4.7–5.5 (12H, m), 6.72 (1H, d, J=8.3 Hz), 6.77–6.9 (2H, m), 6.96 (2H, d, J=8.6 Hz), 7.05 (1H, s), 7.1–7.5 (8H, m), 7.80 (2H, d, J=8.6 Hz), 8.06 (1H, d, J=8.4 Hz), 8.28 (1H, d, J=7 Hz), 8.41 (1H, d, J=7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1305 (M+Na)

Elemental Analysis Calcd. for $C_{58}H_{78}N_{10}O_{21}S.8H_2O$: C 48.80, H 6.64, N 9.81 Found: C 48.88, H 6.50, N 9.81

Example 78

IR (KBr): 1673.9, 1646.9, 1510.0 1238.1 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.4 Hz), 0.96 (3H, d, J=6.6 Hz), 1.05 (3H, d, J=5.6 Hz), 1.2–1.5 (6H, m), 1.5–2.0 (9H, m), 2.1–2.8 (11H, m), 3.1–3.4 (5H, m), 3.4–4.5 (17H, m), 4.6–5.5 (12H, m), 6.6–7.0 (9H, m), 7.04 (1H, s), 7.2–7.5 (3H, m), 7.78 (2H, d, J=8.7 Hz), 8.05 (1H, d, J=8.4 Hz), 8.24 (1H, d, J=7 Hz), 8.39 (1H, d, J=7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1326 (M^+–SO_3+Na)

Elemental Analysis Calcd. for $C_{63}H_{89}N_{11}O_{22}S.9H_2O$: C 48.92, H 6.97, N 9.96 Found: C 48.77, H 6.73, N 9.94

Example 74

IR (KBr): 3450, 1670.1, 1631.5, 1280.5 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=7.0 Hz), 0.96 (3H, t, J=6.8 Hz), 1.05 (3H, d, J=5.6 Hz), 1.1–1.65 (13H, m), 1.65–2.1 (7H, m), 2.1–2.65 (5H, m), 3.17 (1H, m), 3.6–4.5 (13H, m), 4.7–5.3 (11H, m), 5.49 (1H, d, J=5.9 Hz), 6.72 (1H, d, J=8.2 Hz), 6.82 (1H, d, J=8.2 Hz), 6.84 (1H, s), 7.04 (1H, s), 7.29 (2H, d, J=8.3 Hz), 7.2–7.5 (3H, m), 7.80 (2H, d, J=8.3 Hz), 8.10 (1H, d, J=8.4 Hz), 8.26 (1H, d, J=7 Hz), 8.65 (1H, d, J=7 Hz), 8.84 (1H, s)

FAB-MASS: m/z=1237 (M+Na)

Elemental Analysis Calcd. for $C_{53}H_{75}N_8O_{21}SNa.6H_2O$: C 48.10, H 6.63, N 8.47 Found: C 48.26, H 6.62, N 8.46

Example 75

IR (KBr): 3400, 1670.1, 1627.6, 1272.8 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=3.3 Hz), 1.08 (3H, d, J=5.7 Hz), 1.2–1.6 (10H, m), 1.6–2.1 (5H, m), 2.1–2.7 (4H, m), 3.0–3.3 (1H, m), 3.20 (3H, s), 3.29 (2H, t, J=6.4 Hz), 3.73 (2H, m), 3.9–4.6 (13H, m), 4.7–5.3 (11H, m), 5.53 (1H, d, J=5.8 Hz), 6.73 (1H, d, J=8.3 Hz), 6.83 (1H, d, J=8.3 Hz), 6.91 (1H, s), 7.05 (1H, s), 7.23 (1H, dd, J=9.0 and 2.3 Hz), 7.3–7.5 (4H, m), 7.8–8.0 (3H, m), 8.09 (1H, d, J=8.4 Hz), 8.33 (1H, d, J=7 Hz), 8.44 (1H, s), 8.80 (1H, d, J=7 Hz), 8.85 (1H, s)

FAB-MASS: M/z=1293 (M+Na)

Elemental Analysis Calcd. for $C_{55}H_{75}N_8O_{23}SNa.6H_2O$: C 47.89, H 6.36, N 8.12 Found: C 47.81, H 6.26, N 8.05

Example 76

IR (KBr): 3361.3, 1668.1, 1635.3, 1627.6 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.09 (3H, d, J=5.8 Hz), 1.19–1.25 (8H, m), 1.25–2.00 (5H, m), 2.02–2.53 (4H, m), 2.44 (3H, s), 2.61 (2H, t, J=7.6 Hz), 3.05–3.27 (1H, m), 3.55–4.50 (13H, m), 4.65–5.65 (12H, m), 6.42 (1H, s), 6.65–6.95 (3H, m), 7.05 (1H, d, J=0.4 Hz), 7.13–7.50 (5H, m), 7.50–7.88 (6H, m), 8.10 (1H, d, J=9.0 Hz), 8.25 (1H, d, J=8.4 Hz), 8.40 (1H, d, J=7.0 Hz), 8.85 (1H, s)

FAB-MASS: m/z=1299.3 (M+Na–1)

Elemental Analysis Calcd. for $C_{58}H_{77}N_8NaO_{21}S.5H_2O$: C 50.94, H 6.41, N 8.19 Found: C 50.99, H 6.40, N 8.15

Example 77

IR (Nujol): 3351.7, 1670.1, 1652.7, 1623.8 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.06 (3H, d, J=5.8 H z), 1.13–1.45 (8H, m), 1.47–1.96 (5H, m), 2.06–2.66 (8H, m), 2.81 (2H, t, J=7.6 Hz), 3.04–3.30 (1H, m), 3.53–4.50 (13H, m), 4.53–5.70 (12H, m), 6.64–6.88 (3H, m), 7.04 (1H, d, J=0.4 Hz), 7.13–7.60 (11H, m), 8.10 (1H, d, J=9.0 Hz), 8.18 (1H, d, J=8.4 Hz), 8.30 (1H, d, J=7.0 Hz), 8.85 (1H, s)

FAB-MASS: m/z=1287.4 (M+Na–1)

Elemental Analysis Calcd. for $C_{57}H_{77}N_8NaO_{21}S.5H_2O$: C 50.51, H 6.46, N 8.27 Found: C 50.84, H 6.60, N 8.33

Example 78

IR (KBr): 3361.3, 1683.6, 1670.1, 1662.3, 1652.7, 1646.9, 1635.3, 1627.6, 1623.8 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.7 Hz), 1.07 (3H, d, J=5.6 Hz), 1.28–2.00 (13H, m), 2.08–2.60 (4H, m), 3.07–3.30 (1H, m), 3.60–4.66 (17H, m), 4.66–5.12 (9H, m), 5.11 (1H, d, J=3.1 H z), 5.25 (1H, d, J=4.6 Hz), 5.52 (1H, d, J=6.0 Hz), 6.62–6.95 (4H, m), 6.95–7.15 (3H, m), 7.20–7.50 (3H, m), 7.50–7.85 (7H, m), 8.12 (1H, d, J=8.4 Hz), 8.35 (1H, d, J=7.7 Hz), 8.53 (1H, d, J=7.0 Hz), 8.85 (1H, s)

FAB-MASS: m/z=1319.7 (M+Na–1)

Elemental Analysis Calcd. for $C_{57}H_{74}N_8NaO_{22}SF.8H_2O$: C 47.49, H 6.29, N 7.77 Found: C 47.79, H 6.16, N 7.93

Example 79

IR (KBr): 3354.9, 1668.1, 1662.3, 1654.6, 1646.9, 1627.6 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.7 Hz), 0.90–1.10 (6H, m), 1.10–1.40 (8H, m), 1.48–1.95 (5H, m), 2.05–2.46 (4H, m), 2.60 (2H, t, J=7.6 Hz), 3.07–3.23 (1H, m), 3.55–4.45 (14H, m), 4.67–5.32 (11H, m), 5.48–5.63 (1H, m) 6.22 (1H, J=5.3 Hz), 6.65–6.89 (3H, m), 6.97–7.15 (2H, m), 7.20–7.68 (10H, m), 7.85–8.20 (3H, m), 8.84 (1H, s)

FAB-MASS: m/z=1289.4 (M+Na–1)

Elemental Analysis Calcd. for $C_{56}H_{75}N_8NaO_{22}S.3H_2O$: C 50.90, H 6.18, N 8.48 Found: C 50.80, H 6.44, N 8.29

Example 80

IR (KBr): 3361.3, 1664.3, 1631.5, 1600.6 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 H z), 0.98 (3H, d, J=6.7 Hz), 1.16 (3H, t, J=5.9 Hz), 1.20–1.45 (8H, m), 1.50–1.70 (2H, m), 1.70–2.05 (3H, m), 2.10–2.57 (4H, m), 2.63 (2H, t, J=7.6 Hz), 3.10–3.30 (1H, m), 3.68–4.50 (13H, m), 4.78–5.32 (11H, m), 5.66 (1H, d, J=5.7 Hz), 6.68–7.02 (3H, m), 7.04 (1H, d, J=0.4 Hz), 7.25–7.48 (4H, m), 7.60–8.08 (7H, m), 8.10 (1H, d, J=8.4 Hz), 8.28 (1H, d, J=7.7 Hz), 8.85 (1H, s), 9.30 (1H, d, J=7.1 Hz)

FAB-MASS: m/z=1287.5 (M+Na–1)

Elemental Analysis Calcd. for $C_{55}H_{73}N_8NaO_{22}S.3H_2O$: C 50.53, H 6.09, N 8.57 Found: C 50.66, H 6.01, N 8.22

Example 81

IR (KBr): 3349.7, 1668.1, 1627.6 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.09 (3H, d, J=5.8 Hz), 1.18–1.48 (8H, m), 1.50–2.10 (5H, m), 2.10–2.45 (3H, m), 2.50–2.65 (1H, m), 2.77 (2H, t, J=7.6 Hz), 3.05–3.25 (1H, m), 3.60–4.65 (13H, m), 4.67–5.60 (12H, m), 6.65–6.97 (3H, m), 7.05 (1H, d, J=0.4 Hz), 7.21–7.43 (4H, m), 7.76 (1H, s), 7.83–8.05 (3H, m), 8.10 (1H, d, J=9.0 Hz), 8.29 (1H, d, J=8.4 Hz), 8.48 (1H, s), 8.64–9.03 (2H, m)

FAB-MASS: m/z=1233.0 (M+Na–1)

Elemental Analysis Calcd. for $C_{53}H_{71}N_8NaO_{20}S.3H_2O$: C 50.96, H 6.22, N 8.96 Found: C 50.62, H 6.40, N 8.92

Example 82

IR (KBr): 3361.3, 1670.1, 1627.6 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.09 (3 H, d, J=6.9 Hz), 1.18–1.43 (6 H, m), 1.5–2.10 (5 H, m), 2.10–2.69 (4 H, m), 2.77 (2 H, t, J=7.6 Hz), 3.07–3.29 ; (1 H, m), 3.60–4.62 (13 H, m), 4.69–5.23 (10 H, m), 5.27 (1 H, d, J=4.5 Hz), 5.55 (1 H, d, J=5.9 Hz), 6.68–7.00 (3 H, m), 7.05 (1 H, d, J=0.4 Hz), 7.25–7.53 (4 H, m), 7.76 (1 H, s), 7.84–8.05 (3 H, m), 8.13 (1 H, d, J=8.4 Hz), 8.33 (1 H, d, J=7.7 Hz), 8.48 (1 H, s), 8.73–9.00 (2 H, m)

FAB-MASS: m/z=1219.4 (M+Na–1)

Elemental Analysis Calcd. for $C_{52}H_{69}N_8NaO_{21}S{\cdot}5H_2O$: C 48.51, H 6.19, N 8.71 Found: C 48.67, H 6.34, N 8.74

Example 83

IR (KBr): 3357.5, 1668.1, 1627.6 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3 H, d, J=6.7 Hz), 1.07 (3 H, d, J=6.0 Hz), 1.20–1.62 (10 H, m), 1.62–2.00 (5 H, m), 2.10–2.65 (4 H, m), 3.20 (3 H, s), 3.08–3.45 (1 H, m), 3.28 (2 H, t, J=6.5 Hz), 3.53–4.50 (15 H, m), 4.68–5.13 (9 H, m), 5.17 (1 H, d, J=3.1 Hz), 5.25 (1 H, d, J=4.4 Hz), 5.53 (1 H, d, J=6.0 Hz), 6.68–6.95 (4 H, m), 6.95–7.11 (3 H, m), 7.20–7.52 (3 H, m), 7.55–7.95 (7 H, m), 8.13 (1 H, d, J=8.4 Hz), 8.30 (1 H, d, J=7.7 Hz), 8.52 (1 H, d, J=7.0 Hz), 8.85 (1 H, s)

FAB-MASS: m/z=1345.2 (M+Na–1)

Elemental Analysis Calcd. for $C_{59}H_{79}N_8NaO_{23}S{\cdot}8H_2O$: C 48.29, H 6.53, N 7.64 Found: C 48.44, H 6.58, N 7.75

Example 84

IR (KBr): 3353.6, 1662.3, 1627.6 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3 H, d, J=6.7 Hz), 1.07 (3 H, d, J=5.5 Hz), 1.40–1.65 (2 H, m), 1.65–2.00 (5 H, m), 2.00–2.67 (6 H, m), 3.08–3.30 (1 H, m), 3.50–4.50 (15 H, m), 4.68–5.13 (11 H, m), 5.18 (1 H, d, J=3.1 Hz), 5.26 (1 H, d, J=4.5 Hz), 5.53 (1 H, d, J=6.0 Hz), 5.70–6.00 (1 H, m), 6.63–6.95 (4 H, m), 6.95–7.13 (3 H, m), 7.20–7.52 (3 H, m), 7.52–7.95 (7 H, m), 8.12 (1 H, d, J=8.4 Hz), 8.31 (1 H, d, J=7.7 Hz), 8.53 (1 H, d, J=7.0 Hz), 8.85 (1 H, s)

FAB-MASS: m/z=1285.4 (M+N–1) Elemental Analysis Calcd. for $C_{56}H_{71}N_8O_{22}SNa·8H_2O$: C 47.79, H 6.23, N 7.96 Found: C 47.59, H 6.32, N 8.06

Example 85

IR (KBr): 3363.2, 1670.1, 1627.6 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (6 H, d, J=6.5 Hz), 0.96 (3 H, d, J=6.7 Hz), 1.07 (3 H, d, J=5.7 Hz), 1.22–1.41 (2 H, m), 1.50–1.97 (6 H, m), 2.11–2.65 (4 H, m), 3.10–3.30 (1 H, m), 3.60–4.50 (15 H, m), 4.70–5.08 (8 H, m), 5.10 (1 H, d, J=5.6 Hz), 5.16 (1 H, d, J=3.1 Hz), 5.25 (1 H, d, J=4.5 Hz), 5.50 (1 H, d, J=5.9 Hz), 6.65–6.92 (4 H,m), 6.92–7.12 (3 H, m), 7.21–7.50 (3 H, m), 7.52–7.90 (7 H, m), 8.12 (1 H, d, J=8.4 Hz), 8.30 (1 H, d, J=7.7 Hz), 8.56 (1 H, d, J=7.0 Hz), 8.85 (1 H, s)

FAB-MASS: m/z=1287.6 (M+Na–1)

Elemental Analysis Calcd. for $C_{56}H_{73}N_8NaO_{22}S·6.5H_2O$: C 48.66, H 6.27, N 8.11 Found: C 48.67, H 6.32, N 8.20

Example 86

IR (KBr): 3361.3, 1683.6, 1670.1, 1654.6, 1635.3, 1623.8 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3 H, d, J=6.7 Hz), 1.07 (3 H, d, J=5.6 Hz), 1.30–2.00 (11 H, m), 2.10–2.70 (4 H, m), 3.05–3.15 (1 H, m), 3.55–4.70 (17 H, m), 4.70–5.11 (9 H, m), 5.16 (1 H, d, J=3.1 Hz), 5.25 (1 H, d, J=4.5 Hz), 5.52 (1 H, d, J=6.0 Hz), 6.65–6.95 (4 H, m), 6.95–7.10 (3 H, m), 7.10–7.50 (3 H, m), 7.50–7.85 (7 H, m), 8.12 (1 H, d, J=8.4 Hz), 8.30 (1 H, d, J=8.3 Hz), 8.52 (1 H, d, J=7.0 Hz), 8.85 (1 H, s)

FAB-MASS: m/z=1305.2 (M+Na–1)

Elemental Analysis Calcd. for $C_{56}H_{72}N_8NaO_{22}SF·6H_2O$: C 48.34, H 6.09, N 8.05 Found: C 48.47, H 6.29, N 7.95

Example 87

IR (KBr): 3359.4, 1668.1, 1654.6, 1625.7 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3 H, d, J=6.7 Hz), 1.07 (3 H, d, J=6.0 Hz), 1.22–1.62 (6 H, m), 1.62–2.00 (5 H, m), 2.10–2.65 (4 H, m), 3.20 (3 H, s), 3.05–3.40 (1 H, m), 3.31 (2 H, t, J=6.5 Hz), 3.60–4.55 (15 H, m), 4.65–5.13 (9 H, m), 5.16 (1 H, d, J–3.1 Hz), 5.26 (1 H, d, J=4.4 Hz), 5.53 (1 H, d, J=6.0 Hz), 6.68–6.95 (4 H, m), 6.95–7.20 (3 H, m), 7.20–7.58 (3 H, m), 7.58–7.90 (7 H, m), 8.13 (1 H, d, J=8.4 Hz), 8.32 (1 H, d, J=7.7 Hz), 8.53 (1 H, d, J=7.0 Hz), 8.85 (1 H, s)

FAB-MASS: m/z=1317.6 (M+Na–1)

Elemental Analysis Calcd. for $C_{57}H_{75}N_8NaO_{23}S·7H_2O$: C 48.16, H 6.31, N 7.88 Found: C 48.21, H 6.60, N 7.78

Example 88

IR (KBr): 3350, 2954, 1668, 1629, 1538, 1511, 1454, 1249 cm^{-1}

NMR (DMSO-d_6, δ): 0.88 (3 H, t, J=7.1 Hz), 0.96 (3 H, d, J=7.5 Hz), 1.08 (2 H, d, J=5.7 Hz), 1.2–1.5 (6 H, m), 1.6–2.4 (8 H, m), 2.6–2.7 (1 H, m), 3.1–3.3 (1 H, m), 3.6–4.5 (19 H, m), 4.7–5.3 (8 H, m), 6.73 (1 H, d, J=8.2 Hz), 6.8–7.1 (5 H, m), 7.19 (1 H, s), 7.3–7.5 (3 H, m), 7.75 (2 H, d, J=8.7 Hz), 7.8–8.0 (4 H, m), 8.08 (1 H, d, J=8.9 Hz), 8.30 (1 H, d, J=7.7 Hz), 8.7–9.0 (3 H, m)

FAB-MASS: m/z=1327 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{57}H_{73}N_{10}O_{22}NaS·9H_2O$: C 46.65, H 6.25, N 9.54 Found: C 46.95, H 6.22, N 9.55

Example 89

IR (KBr): 3376, 2931, 2858, 1662, 1631, 1521, 1444, 1245, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3 H, d, J=6.7 Hz), 1.09 (3 H, d, J=5.9 Hz), 1.3–1.6 (6 H, m), 1.7–2.1 (5 H, m), 2.2–2.4 (3 H, m), 2.5–2.6 (1 H, m), 3.21 (3 H, s), 3.2–3.4 (3 H, m), 3.6–4.5 (16 H, m), 4.79 (2 H, d, J=6.0 Hz), 4.9–5.2 (5 H, m), 5.10 (1 H, d, J=3.6 Hz), 5.18 (1 H, d, J=3.1 Hz), 5.26 (1 H, d, J=4.5 Hz), 5.53 (1 H, d, J=6.0 Hz), 6.73 (1 H, d, J=8.2 Hz), 6.8–7.0 (2 H, m), 7.0–7.2 (3 H, m), 7.3–7.5 (3 H, m), 7.6–7.9 (8 H, m), 8.01 (2 H, d, J=8.4 Hz), 8.12 (1 H, d, J=8.4 Hz), 8.31 (1 H, d, J=7.7 Hz), 8.79 (1 H, d, J=7.0 Hz), 8.85 (1 H, s)

FAB-MASS: m/z=1367 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{61}H_{77}N_8O_{23}NaS·6.5H_2O$: C 50.10, H 6.20, N 7.66 Found: C 50.09, H 6.17, N 7.62

Example 90

IR (KBr): 3363, 2937, 2869, 1646, 1444, 1255 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3 H, d, J=6.7 Hz), 1.08 (3 H, d, J=5.7 Hz), 1.2–1.6 (10 H, m), 1.7–2.1 (5 H, m), 2.1–2.4 (3 H, m), 2.5–2.7 (1 H, m), 3.20 (3 H, s), 3.2–3.4 (1 H, m), 3.6–4.6 (16 H, m), 4.7–5.2 (8 H, m), 5.16 (1 H, d, J=3.1 Hz), 5.24 (1 H, d, J=4.5 Hz), 5.54 (1 H, d, J=5.8 Hz), 6.73 (1 H, d, J=8.2 Hz), 6.8–7.0 (2 H, m), 7.1–7.4 (6 H, m), 7.97 (2 H, d, J=8.8 Hz), 8.0–8.4 (6 H, m), 8.84 (1 H, s), 8.92 (1 H, d, J=7.0 Hz)

FAB-MASS: m/z=1403.6 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{59}H_{77}N_{10}O_{23}NaS_2·6H_2O$: C 47.58, H 6.02, N 9.40 Found: C 47.72, H 6.12, N 9.42

Example 91

IR (KBr): 3350, 1668, 1654, 1625, 1537, 1521, 1245, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.9–1.1 (6 H, m),1.07 (3 H, d, J=5.7 Hz), 1.4–2.0 (7 H, m), 2.2–2.5 (3 H, m), 2.5–2.6 (1 H, m), 3.1–3.3 (1 H, m), 3.6–4.5 (16 H, m), 4.7–5.1 (7 H, m), 5.09 (1 H, d, J=5.6 Hz), 5.16 (1 H, d, J=3.1 Hz), 5.25 (1 H, d, J=4.4 Hz), 5.53 (1 H, d, J=6.0 Hz), 6.73 (1 H, d, J=8.4 Hz), 6.8–7.2 (6 H, m) 7.2–7.5 (4 H, m), 7.5–7.8 (6 H, m), 8.11 (1 H, d, J=8.4 Hz), 8.32 (1 H, d, J=7.7 Hz), 8.54 (1 H, d, J=7.0 Hz), 8.84 (1 H, s)

FAB-MASS: m/z=1259 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{54}H_{69}N_8O_{22}NaS·8H_2O$: C 46.95, H 6.20, N 8.11 Found: C 47.20, H 6.23, N 8.28

Example 92

IR (KBr): 3359, 2929, 2852, 1668, 1650, 1631, 1538, 1515 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3 H, d, J=6.7 Hz), 1.09 (3 H, d, J=6.1 Hz), 1.2–1.6 (5 H, m), 1.6–2.5 (10 H, m), 2.5–2.6 (1 H, m), 3.18 (1 H, m), 3.7–4.5 (15 H, m), 4.8–5.2 (8 H, m), 5.17 (1 H, d, J=3.1 Hz), 5.26 (1 H, d, J=4.5 Hz), 5.55 (1 H, d, J=5.9 Hz), 6.73 (1 H, d, J=8.1 Hz), 6.81 (1 H, s), 6.85 (1

H, s), 7.05 (1 H, s), 7.2–7.4 (3 H, m), 7.45 (2 H, d, J=8.2 Hz), 7.96 (2 H, d, J=8.2 Hz), 8.0–8.2 (4 H, s), 8.2–8.3 (1 H, m), 8.85 (1 H, s), 8.9–9.0 (1 H, d, J=7.0 Hz)

FAB-MASS: m/z=1327.5 $(M+Na)^+$

Elemental Analysis Calcd. for $C_{56}H_{69}N_{10}O_{21}S_2Na \cdot 6H_2O$: C 47.59, H 5.78, N 9.91 Found: C47.89, H 5.76, N 9.93

Example 93

IR (KBr): 3350, 1654, 1629, 1517, 1249, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.9–1.1 (6 H, m), 1.11 (3 H, d, J=5.9 Hz), 1.6–2.0 (5 H, s), 2.1–2.4 (3 H, s), 2.6–2.7 (1 H, m), 3.1–3.3 (1 H, m), 3.6–4.5 (16 H, m), 4.7–5.2 (7 H, m), 5.10 (1 H, d, J=5.6 Hz), 5.17 (1 H, d, J=3.1 Hz), 5.25 (1 H, d, J=4.5 Hz), 5.55 (1 H, d, J=5.7 Hz), 6.7–6.9 (3 H, m), 7.0–7.5 (6 H, m), 7.74 (2 H, d, J=8.8 Hz), 7.91 (2 H, d, J=8.5 Hz), 8.1–8.4 (8 H, m), 8.84 (1 H, s), 8.97 (1 H, d, J=7.0 Hz)

FAB-MASS: m/z=1363.5 $(M+Na)^+$

Elemental Analysis Calcd. for $C_{59}H_{69}N_{10}O_{23}SNa \cdot 5H_2O$: C 49.51, H 5.56, N 9.79 Found: C 49.39, H 5.63, N 9.77

Example 94

IR (KBr): 3355, 2929, 2856, 1664, 1631, 1519, 1440, 1282 cm^{-1}

NMR (DMSO-d_6, δ): 0.84 (3 H, t, J=6.7 Hz), 0.96 (3 H, d, J=6.7 Hz), 1.07 (3 H, t, J=5.8 Hz), 1.2–1.5 (12 H, m), 1.7–2.0 (5 H, m), 2.2–2.4 (3 H, m), 2.5–2.7 (1 H, m), 2.94 (2 H, t, J=7.4 Hz), 3.1–3.3 (1 H, m), 3.6–4.6 (14 H, m), 4.8–5.2 (7 H, m), 5.10 (1 H, d, J=3.6 Hz), 5.17 (1 H, d, J=3.1 Hz), 5.26 (1 H, d, J=4.5 Hz), 5.55 (1 H, d, J=5.9 Hz), 6.73 (1 H, d, J=8.2 Hz), 6.8–7.0 (2 H, m), 7.0–7.5 (4 H, m), 8.0–8.2 (5 H, m), 8.27 (1 H, d, J=7.7 Hz), 8.85 (1 H, s), 8.93 (1 H, d, J=7.0 Hz)

FAB-MASS: m/z=1279 $(M+Na^+)$

Elemental Analysis Calcd. for $C_{53}H_{73}N_{10}O_{22}SNa \cdot 5.5H_2O$: C 46.93, H 6.24, N 10.33 Found: C 46.93, H 6.46, N 10.31

Example 95

IR (KBr): 3363, 1673, 1648, 1538, 1252 cm^{-1}

NMR (DMSO-d_6, δ): 0.92 (3 H, t, J=6.8 Hz), 0.97 (3 H, d, J=6.8 Hz), 1.10 (3 H, d, J=5.8 Hz), 1.2–1.5 (6 H, m), 1.7–2.1 (5 H, m), 2.1–2.4 (3 H, m), 2.5–2.6 (1 H, m), 3.1–3.3 (1 H, m), 3.6–4.5 (16 H, m), 4.7–5.1 (9 H, m), 5.16 (1 H, d, J=3.1 Hz), 5.24 (1 H, d, J=4.5 Hz), 5.54 (1 H, d, J=5.8 Hz), 6.73 (1 H, d, J=8.2 Hz), 6.8–7.4 (8 H, m), 8.04 (2 H, d, J=8.8 Hz), 8.13 (2 H, d, J=8.6 Hz), 8.2–8.4 (4 H, m), 8.84 (1 H, s), 8.98 (1 H, d, J=7.0 Hz)

FAB-MASS: m/z=1329.6 $(M+Na)^+$

Elemental Analysis Calcd. for $C_{56}H_{71}N_{10}O_{23}SNa \cdot 7H_2O$: C 46.92, H 5.97, N 9.77 Found: C 46.86, H 5.99, N 9.77

Example 96

Ir (KBr): 3355, 2929, 1666, 1648, 1631, 1515, 1442, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3 H, t, J=6.7 Hz), 0.97 (3 H, d, J=6.7 Hz), 1.10 (3 H, d, J=5.8 Hz), 1.2–1.5 (10 H, m), 1.7–2.1 (5 H, m), 2.1–2.4 (3 H, m), 2.5–2.6 (1 H, m), 3.1–3.3 (1 H, m), 3.6–4.6 (16 H, m), 4.79 (2 H, d, J=5.9 Hz), 4.8–5.2 (5 H, m), 5.09 (1 H, d, J=5.5 Hz), 5.16 (1 H, d, J=3.1 Hz), 5.23 (1 H, d, J=4.5 Hz), 5.52 (1 H, d, J=5.9 Hz), 6.73 (1 H, d, J=8.0 Hz), 6.8–6.9 (2 H, m), 7.0–7.5 (6 H, m), 7.97 (2 H, d, J=8.8 Hz), 8.0–8.3 (6 H, m), 8.83 (1 H, s), 8.88 (1 H, d, J=7.0 Hz)

FAB-MASS: m/z=1373.5 $(M+Na)^+$

Elemental Analysis Calcd. for $C_{58}H_{75}N_{10}O_{22}S_2Na \cdot 6H_2O$: C 47.73, H 6.01, N 9.60 Found: C 47.57, H 5.92, N 9.53

Example 97

IR (KBr): 3361, 2925, 2852, 1668, 1650, 1631, 1538, 1452, 1049 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3 H, t, J=6.9 Hz), 0.96 (3 H, d, J=6.7 Hz), 1.08 (3 H, d, J=5.7 Hz), 1.2–1.4 (11 H, m), 1.4–1.6 (2 H, m), 1.7–2.1 (5 H, m), 2.1–2.5 (5 H, m), 2.5–2.6 (1 H, m), 3.1–3.3 (2 H, m), 3.7–4.5 (14 H, m), 4.7–5.0 (7 H, m), 5.09 (1 H, d, J=5.6 Hz), 5.16 (1 H, d, J=3.1 Hz), 5.25 (1 H, d, J=4.5 Hz), 5.54 (1 H, d, J=5.8 Hz), 6.73 (1 H, d, J=8.2 Hz), 6.8–7.0 (2 H, d), 7.04 (1 H, s), 7.2–7.5 (3 H, m), 8.03 (4 H, s), 8.0–8.3 (2 H, m), 8.84 (1 H, s), 8.95 (1 H, d, J=7.0 Hz)

FAB-MASS: m/z=1321.0 $(M+Na)^+$

Elemental Analysis Calcd. for $C_{55}H_{75}N_{10}O_{21}S_2Na \cdot 5H_2O$: C 47.54, H 6.17, N 10.08 Found: C 47.38, H 6.12, N 9.98

Example 98

IR (KBr): 3374, 2937, 2875, 1658, 1629, 1531, 1436, 1255, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.9–1.11 (6 H, m), 1.09 (3 H, d, J=5.7 Hz), 1.2–1.5 (4 H, m), 1.7–2.1 (5 H, m), 2.2–2.5 (3 H, m), 2.6–2.7 (1 H, m), 3.2–3.3 (1 H, m), 3.6–4.5 (16 H, m), 4.80 (2 H, d, J=5.8 Hz), 4.8–5.2 (5 H, m), 5.10 (1 H, d, J=5.5 Hz), 5.17 (1 H, d, J=3.0 Hz), 5.24 (1 H, d, J=4.5 Hz), 5.53 (1 H, d, J=5.8 Hz), 6.73 (1 H, d, J=8.2 Hz), 6.8–7.0 (2 H, m), 7.06 (1 H, s), 7.10 (2 H, d, J=8.9 Hz), 7.2–7.5 (3 H, m), 7.68 (1 H, s), 7.86 (2 H, d, J=8.8 Hz), 8.0–8.4 (6 H, m), 8.84 (1 H, s), 8.90 (1 H, d, J=7.0 Hz)

FAB-MASS: m/z=1314 $(M+Na^+)$

Elemental Analysis Calcd. for $C_{56}H_{70}N_9O_{23}NaS \cdot 6H_2O$: C 48.03, H 5.90, N 9.00 Found: C 47.92, H 5.83, N 8.88

Example 99

IR (KBr): 3345, 1646, 1633, 1531, 1257 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3 H, d, J=6.7 Hz), 1.11 (3 H, d, J=5.7 Hz), 1.2–1.6 (10 H, m), 1.7–2.5 (8 H, m), 2.6–2.7 (1 H, m), 3.21 (3 H, s), 3.3–3.4 (1 H, m), 3.7–4.6 (16 H, m), 4.8–5.2 (8 H, m), 5.16 (1 H, d, J=3.1 Hz), 5.24 (1 H, d, J=4.5 Hz), 5.55 (1 H, d, J=5.7), 6.7–6.9 (3 H, m), 7.0–7.5 (6 H, m), 8.0–8.3 (8 H, m), 8.84 (1 H, s), 8.96 (1 H, d, J=7.0 Hz)

FAB-MASS: m/z=1387.7 $(M+Na^+)$

Elemental Analysis Calcd. for $C_{59}H_{77}N_{10}O_{24}NaS \cdot 6H_2O$: C 48.09, H 6.09, N 9.51 Found: C 47.81, H 5.83, N 9.38

Example 100

IR (KBr): 3357, 1668, 1631, 1429, 1284, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3 H, d, J=6.7 Hz), 1.09 (3 H, d, J=5.8 Hz), 1.8–2.4 (6 H, m), 2.5–2.6 (1 H, m), 3.1–3.2 (1 H, m), 3.7–4.6 (14 H, m), 4.7–5.2 (7 H, m), 5.10 (1 H, d, J=5.5 Hz), 5.17 (1 H, d, J=3.1 Hz), 5.24 (1 H, d, J=5.5 Hz), 5.53 (1 H, d, J=5.8 Hz), 6.75 (1 H, d, J=8.2 Hz), 6.8–6.9 (2 H, m), 7.05 (1 H, s), 7.3–7.6 (9 H, m), 7.8–7.9 (4 H, m), 8.0–8.2 (5 H, m), 8.2–8.3 (1 H, m), 8.34 (1 H, d, J=9.3 Hz), 8.7–8.8 (1 H, m), 8.85 (1 H, s)

FAB-MASS: m/z=1332.7 $(M+Na^+)$

Elemental Analysis Calcd. for $C_{58}H_{65}N_{10}O_{22}SNa \cdot 8H_2O$: C 47.93, H 5.62, N 9.64 Found: C 47.83, H 5.53, N 9.56

Example 101

IR (KBr): 3353, 2929, 2856, 1666, 1631, 1612, 1496, 1440, 1259 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3 H, t, J=6.6 Hz), 0.97 (3 H, d, J=6.5 Hz), 1.09 (3 H, d, J=5.9 Hz), 1.2–1.5 (10 H, m), 1.7–2.1 (5 H, m), 2.2–2.5 (3 H, m), 2.6–2.7 (1 H, m), 3.1–3.2 (1 H, m), 3.6–4.5 (16 H, m), 4.7–5.0 (3 H, m), 5.0–5.2 (5 H, m), 5.10 (1 H, d, J=3.1 Hz), 5.26 (1 H, d, J=4.2 Hz), 5.56 (1 H, d, J=5.5 Hz), 6.73 (1 H, d, J=8.1 Hz), 6.8–7.0 (2 H, m), 7.05 (1 H, s), 7.1–7.5 (5 H, m), 8.0–84 (8 H, m), 8.85 (1 H, s), 8.95 (1 H, d, J=7.0 Hz)

FAB-MASS: m/z=1357.3 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{58}H_{75}N_{10}O_{23}NaS\cdot 7H_2O$: C 47.67, H 6.14, N 9.58 Found: C 47.63, H 6.42, N 9.52

Example 102

IR (KBr): 3361, 1670, 1648, 1633, 1540, 1519, 1249 cm^{-1}

NMR (DMSO-d_6, δ): 0.89 (3 H, t, J=7.0 Hz), 0.97 (3 H, d, J=6.8 Hz), 1.10 (3 H, d, J=5.7 Hz), 1.2–1.5 (6 H, m), 1.6–2.4 (8 H, m), 2.5–2.7 (1 H, m), 3.1–3.3 (1 H, m), 3.6–4.5 (16 H, m), 4.80 (2 H, d, J=5.8 Hz), 4.8–5.2 (5 H, m), 5.10 (1 H, d, J=5.4 Hz), 5.18 (1 H, d, J=3.1), 5.25 (1 H, d, J=4.3 Hz), 5.55 (1 H, d, J=5.7 Hz), 6.73 (1 H, d, J=8.2 Hz), 6.8–7.0 (2 H, m), 7.0–7.5 (6 H, m), 8.02 (1 H, d, J=5.3 Hz), 8.0–8.4 (4 H, m), 8.42 (2 H, d, J=8.4 Hz), 8.48 (2 H, d, J=8.9 Hz), 8.8–9.0 (3 H, m)

FAB-MASS: m/z=1339.3 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{58}H_{73}N_{10}O_{22}SNa\cdot 6H_2O$: C 48.87, H 6.01, N 9.83 Found: C 49.16, H 5.92, N 9.86

Example 103

IR (KBr): 3350, 2971, 2859, 1672, 1629, 1537, 1442, 1247, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3 H, d, J=6.8 Hz), 1.0–1.2 (6 H, m), 1.2–1.6 (12 H, m), 1.7–2.5 (8 H, m), 2.5–2.6 (1 H, m), 3.2–3.6 (7 H, m), 3.7–4.5 (16 H, m), 4.76 (2 H, d, J=4.6 Hz), 4.8–5.1 (5H, m), 5.09 (1H, d, J=5.5 Hz), 5.16 (1H, d, J=3.1 Hz), 5.23 (1H, d, J=5.5 Hz), 5.51 (1H, d, J=5.9 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–6.9 (2H, m), 7.0–7.1 (3H, m), 7.3–7.5 (3H, m), 7.67 (2H, d, J=6.9 Hz), 7.71 (2H, d, J=6.9 Hz), 7.95 (2H, d, J=8.4 Hz), 8.05 (1H, d, J=7.0 Hz), 8.23 (1H, d, J=7.7 Hz), 8.70 (1H, d, J=7.0 Hz), 8.04 (1H, s)

FAB-MASS:m/z=1377.1 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{60}H_{83}N_8O_{24}NaS\cdot 5H_2O$:C 49.86, H 6,49, N 7.75 Found:C 49.74, H 6,73, N 7.68

Example 104

IR (KBr): 3349, 2937, 2858, 1672, 1629, 1537, 1444, 1249, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=5.6 Hz), 1.2–1.7 (14H, m), 1.7–2.1 (5H, m) 2.1–2.4 (5H, m), 2.5–2.6 (1H, m), 3.1–3.2 (1H, m), 3.4–3.6 (4H, m), 3.7–4.5 (16H, m), 4.77 (2H, d, j=5.7 Hz), 4.8–5.2 (5H, m), 5.09 (1H, d, J=5.6 Hz), 5.16 (1H, d, J=3.1 Hz), 5.24 (1H, d, J=4.5 Hz), 5.51 (1H, d, J=5.8 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–6.9 (2H, m), 7.0–7.1 (3H, m) 7.3–7.5 (3H, m), 7.6–7.8 (4H, m), 7.96 (2H, d, J=8.4 Hz), 8.10 (1H, d, J=8.4 Hz), 8.24 (1H, d, J=7.7 Hz), 8.71 (1H, d, j=7.0 Hz), 8.89 (1H, s)

FAB-MASS:m/z=1386.5 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{61}H_{82}N_9O_{23}NaS\cdot 6H_2O$:C 49.76, H 6.43, N 8.56 Found:C 49.99, H 6.39, N 8.52

Example 105

IR (KBr): 3350, 2933, 2856, 1664, 1631, 1604, 1511, 1450, 1243, 1045 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.5 Hz), 1,05 (3H, d, J=5.7 Hz), 1.2–1.5 (8H, m), 1.6–2.0 (5H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.0–3.3 (5H, m), 3.6–4.4 (20H, m), 4.7–5.1 (7H, m), 5.10 (1H, d, J=5.5 Hz), 5.16 (1H, d, J=3.1 Hz), 5.27 (1H, d, J=4.5Hz), 5.51 (1H, d, J=6.0 Hz), 6.7–7.1 (9H, m), 7.2–7.5 (3H, m), 8.0–8.2 (2H, m), 8.2–8.4 (1H, m), 8.4–8.6 (1H, m), 8.66 (1H, d, J=2.2 Hz), 8.85 (1H, s)

FAB-MASS:m/z=1360 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{58}H_{80}N_{11}O_{22}SNa\cdot 6H_2O$:C 48.16, H 6.41, N 1065 Found:C 47.91, H 6.31, N 10.56

Example 106

IR (KBr): 3369, 3345, 2935, 1672, 1629, 1511, 1245, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, j=6.7 Hz), 1.06 (3H, d, J=5.8 Hz), 1.3–1.6 (10H, m), 1.6–2.0 (5H, m), 2.1–24 (3H, m), 2.5–2.6 (1H, m), 3.20 (3H, s), 3.28 (2H, t, J=6.4 Hz), 3.1–3.4 (5H, m), 3.7–4.5 (20H, m), 4.7–5.1 (7H, m), 5.08 (1H, d, J=5.5 Hz), 5.15 (1H, d, J=3.1 Hz), 5.23 (1H, d, J=4.5 Hz), 5.48 (1H, d, J=5.8 Hz), 6.73 (1H, d, J=8.2 Hz), 6.82 (2H, d, J=9.1 Hz), 6.94 (2H, d, J=9.1 Hz), 6.9–7.0 (1H, m), 7.04 (1H, s), 7.3–7.5 (3H, m), 8.0–8.1 (2H, m), 8.27 (1H, d, J=7.7 Hz), 8.49 (1H, d, J=7.0 Hz), 8.66 (1H, d, J=2.2 Hz), 8.84 (1H, s)

FAB-MASS:m/z=1404 ($M+Na^+$)

Example 107

IR (KBr): 3357, 1647, 1631, 1537, 1444, 1249, 1049 cm^{-1}

NMR (DMSO-d_6, δ): 0.9–1.1 (6H, m), 1.09 (3H, d, j=5.9 Hz), 1.6–2.4 (8H, m), 2.4–2.5 (1H, m), 3.1–3.3 (1.H, m), 3.6–4.5 (16H, m), 4.8–5.2 (7H, m), 5.10 (1H, d, J=5.6 Hz), 5.17 (1H, d, J=3.1 Hz), 5.25 (1H, d, J=4.5 Hz), 5.55 (1H, d, J=5.9 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–7.0 (2H, m), 7.0–7.6 (6H, m), 7.73 (2H, d, J=8.7 Hz), 7.86 (2H, d, J=8.5 Hz), 8.0–8.3 (8H, m), 8.84 (1H, s), 8.9–9.0 (1H, m)

FAB-MASS:m/z=1379.4 $(M+Na)^+$

Elemental Analysis Calcd. for $C_{59}H_{69}N_{10}O_{22}S_2Na\cdot 6H_2O$:C 48.36, H 5.57, N 9.56 Found:C 48.18, H 5.60, N 9.36

The Object Compounds (108) to (117) were obtained according to a similar manner to that of Example 27.

Example 108

IR (KBr): 3350, 2933, 1670, 1627, 1521, 1436, 1272, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=6.7 Hz), 0.92 (3H, d, J=6.7 Hz), 1.1–1.4 (11H, m), 1.7–2.4 (9H, m), 3.1–3.2 (1H, m), 3.5–5.4 (27H, m), 6.6–7.2 (8H, m), 7.5–7.8 (3H, m), 7.8–8.0 (3H, m), 8.1–8.8 (3H, m)

FAB-MASS:m/z=1249.4 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{52}H_{71}N_{10}O_{21}NaS\cdot 7H_2O$:C 46.15, H 6.33, N 10.35 Found:C 46.12, H 6.35, N 10.24

Example 109

IR (KBr pelet): 3361, 2933, 2856, 1670, 1652, 1616, 1540, 1108, 1448, 1261, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.6 Hz), 0.97 (3H, d, J=6.8 Hz), 1.12 (3H, d, J=6.8 Hz), 1.2–1.5 (10H, m), 1.7–2.0 (5H, m), 2.2–2.6 (4H, m), 3.1–3.2 (1H, m), 3.7–4.4 (16H, m), 4.8–5.3 (10H, m), 5.59 (1H, d, J=6.0 Hz), 6.7–6.9 (3H, m), 7.0–7.4 (7H, m), 7.8–8.2 (4H, m), 8.8–9.0 (2H, m)

FAB-MASS:m/z=1280.3 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{54}H_{72}N_9O_{23}NaS \cdot 7H_2O$:C 46.45, H 6.21, N 9.03 Found:C 46.68, H 6.44, N 9.03

Example 110

IR (KBr): 3350, 2931, 1670, 1627, 1540, 1436, 1276, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.8 Hz), 0.93 (2H, d, J=8.8 Hz), 1.08 (2H, d, J=5.9 Hz), 1.2–1.4 (4H, m), 1.5–1.7 (2H, m), 1.7–2.1 (3H, m), 2.1–2.4 (3H, m), 2.6–2.7 (3H, m), 3.1–3.3 (1H, m), 3.6–4.5 (17H, m), 4.7–5.4 (8H, m), 6.73 (1H, d, J=8.2 Hz), 6.83 (2H, d, J=8.2 Hz), 7.0–7.1 (1H, m), 7.2–7.5 (5H, m), 7.65 (2H, d, J=8.2 Hz), 7.74 (2H, d, J=8.4 Hz), 7.98 (2H, d, J=8.4 Hz), 8.08 (1H, d, J=8.5 Hz), 8.25 (1H, d, J=8.5 Hz), 8.74 (1H, d, J=7.6 Hz), 8.7–9.0 (1H, br)

FAB-MASS:m/z=1232.2 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{53}H_{69}N_8O_{21}NaS \cdot 3H_2O$:C 50.39, H 5.98, N 8.87 Found:C 50.34, H 6.25, N 8.90

Example 111

IR (KBr): 3353.6, 1670.1, 1652.7, 1623. 8 cm^{-1}

NMR (DMSO-d_6, δ): 0.96 (3H, d, J=6.7 Hz), 1.07 (3H, d, J=5.6 Hz), 1.20–1.62 (8H, m), 1.62–2.00 (5H, m), 2.10–2.65 (4H, m), 3.20 (3H, s), 3.08–3.40 (1H, m), 3.30 (2H, t, J=6.5 Hz), 3.53–4.50 (15H, m), 4.68–5.13 (9H, m), 5.16 (1H, d, J=2.9 Hz), 5.26 (1H, d, J=4.5 Hz), 5.53 (1H, d, J=5.9 Hz), 6.68–6.95 (4H, m), 6.95–7.11 (3H, m), 7.20–7.52 (3H, m), 7.55–7.95 (7H, m), 8.13 (1H, d, J=8.4 Hz), 8.31 (1H, d, J=7.7 Hz), 8.53 (1H, d, J=7.0 Hz), 8.85 (1H, s)

FAB-MASS:m/z=1331.5 (M+Na−1)

Elemental Analysis Calcd. for $C_{58}H_{77}N_8NaO_{23}S \cdot 6H_2O$:C 49.15, H 6.33, N 7.91 Found:C 49.07, H 6.53, N 7.84

Example 112

IR (KBr): 3350, 2937, 1673, 1646, 1631, 1538, 1519, 1456, 1247, 1049 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.6 Hz), 1.07 (3H, d, J=5.7 Hz), 1.3–2.4 (25H, m), 2.5–2.6 (1H, m), 3.2–3.4 (1H, m), 3.5–4.6 (20H, m), 4.8–5.7 (11H, m), 6.73 (1H, d, J=8.0 Hz), 6.9–7.0 (2H, m), 7.0–7.2 (3H, m), 7.3–7.6 (3H, m), 7.74 (2H, d, J=8.5 Hz), 7.77 (2H, d, J=8.3 Hz), 8.02 (2H, d, J=8.3 Hz), 8.13 (1H, d, J=8.4 Hz), 8.30 (1H, d, J=7.7 Hz), 8.77 (1H, d, J=7.0 Hz), 8.85 (1H, s)

FAB-MASS:m/z=1389 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{61}H_{83}N_8O_{24}NaS \cdot 7H_2O$:C 49.06, H 6.55, N 7.50 Found:C 49.03, H 6.54, N 7.56

Example 113

NMR (DMSO-d_6, δ): 0.84 (3H, t, J=6.7 Hz), 0.96 (3H, d, J=6.7 Hz), 1.07 (3H, d, J=5.9 Hz), 1.1–1.3 (14H, m), 1.7–2.1 (5H, m), 2.2–2.5 (3H, m), 2.6–2.7 (1H, m), 3.1–3.3 (1H, m), 3.7–4.5 (16H, m), 4.7–5.1 (7H, m), 5.10 (1H, d, J=5.5 Hz), 5.16 (1H, d, J=3.1 Hz), 5.25 (1H, d, J=4.5 Hz), 5.49 (1H, d, J=5.7 Hz), 6.53 (1H, d, J=3.1 Hz), 6.73 (1H, d, J=8.2 Hz), 6.8–6.9 (2H, m), 7.05 (1H, m), 7.31 (1H, d, J=8.1 Hz), 7.4–7.6 (4H, m), 7.70 (1H, d, J=6.7 Hz), 8.08 (1H, d, J=8.4 Hz), 8.18 (1H, s), 8.31 (1H, d, J=7.7 Hz), 8.57 (1H, d, J=7.0 Hz), 8.85 (1H, s)

FAB-MASS:m/z=1264 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{54}H_{76}N_9O_{21}NaS \cdot 6H_2O$:C 48.03, H 6.57, N 9.34 Found:C 48.02, H 6.61, N 9.28

Example 114

IR (KBr): 3350, 2937, 1668, 1631, 1537, 1247, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.85 (3H, t, J=7.4 Hz), 0.96 (3H, d, J=6.5 Hz), 1.07 (3H, d, J=5.7 Hz), 1.3–1.7 (7H, m), 1.7–2.1 (5H, m), 2.2–2.4 (3H, m), 2.6–2.7 (1H, m), 3.0–3.8 (16H, m), 3.8–4.6 (11H, m), 4.7–5.3 (6H, m), 6.73 (1H, d, J=8.2 Hz), 6.8–7.0 (2H, m), 7.0–7.2 (3H, m), 7.3–7.5 (3H, m), 7.6–7.8 (4H, m), 7.96 (2H, d, J=8.3 Hz), 8.11 (1H, d, J=8.2 Hz), 8.26 (1H, d, J=7.6 Hz), 8.6–9.0 (2H, m)

FAB-MASS:m/z=1319.4 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{57}H_{77}N_8O_{23}NaS \cdot 8H_2O$:C 47.50, H 6.50, N 7.77 Found:C 47.72, H 6.85, N 7.85

Example 115

IR (Kbr): 3350, 1666, 1631, 1546, 1276, 1247 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3H, d, J=7.5 Hz), 1.08 (3H, d, J=5.7 Hz), 1.4–1.6 (4H, m), 1.6–2.1 (5H, m), 2.1–2.4 (3H, m), 2.5–2.6 (1H, m), 3.1–3.3 (1H, m), 3.23 (3H, s), 3.3–3.5 (2H, m), 3.7–4.5 (16H, m), 4.79 (2H, d, J=6.2 Hz), 4.8–5.1 (5H, m), 5.11 (1H, d, J=5.6 Hz), 5.18 (1H, d, J=3.1 Hz), 5.26 (1H, d, J=4.4 Hz), 5.54 (1H, d, J=5.7 Hz), 6.73 (1H, d, J=8.1 Hz), 6.8–7.0 (2H, m), 7.0–7.1 (3H, m), 7.3–7.5 (3H, m), 7.6–7.9 (8H, m), 8.01 (2H, d, J=8.4 Hz), 8.08 (1H, d, J=8.4 Hz), 8.32 (1H, d, J=7.7 Hz), 8.80 (1H, d, J=7.0 Hz), 8.85 (1H, s)

FAB-MASS:m/z=1353.9 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{60}H_{75}N_8O_{23}NaS \cdot 9.5H_2O$:C 47.96, H 6.31, N 7.46 Found:C 47.97, H 6.25, N 7.41

Example 116

IR (KBr): 3450, 2935, 1675, 1650, 1540, 1513, 1454, 1057 cm^{-1}

NMR (DMSO-d_6, δ): 0.97 (3H, d, J=6.7 Hz), 1.09 (3H, d, J=5.9 Hz), 1.60 (6H, s), 1.7–2.4 (6H, m), 2.5–2.6 (1H, m), 3.1–3.6 (5H, m), 3.7–4.5 (14H, m), 4.7–5.0 (3H, m), 5.0–5.2 (4H, m), 5.11 (1H, d, J=5.5 Hz), 5.18 (1H, d, J=3.1 Hz), 5.26 (1H, d, J=4.5 Hz), 5.56 (1H, d, J=6.0 Hz), 6.8–7.5 (9H, m), 7.84 (2H, d, J=8.8), 8.0–8.4 (6H, m), 8.85 (1H, s), 8.91 (1H, d, J=7.0 Hz)

FAB-MASS:m/z=1328 $(M+Na)^+$

Elemental Analysis Calcd. for $C_{55}H_{68}N_{11}O_{21}S_2Na \cdot 8H_2O$:C 45.55, H 5.84, N 10.62 Found:C 45.62, H 5.70, N 10.54

Example 117

IR (KBr): 3350, 2939, 1664, 1627, 1531, 1446, 1249, 1049 cm^{-1}

NMR (DMSO-d_6, δ): 0.8–1.0 (6H, m), 1.4–1.9 (9H, m), 2.0–2.5 (4H, m), 3.1–3.2 (1H, m), 3.22 (3H, s), 3.3–3.4 (2H, m), 3.51 (2H, s), 3.6–4.4 (16H, m), 4.7–5.2 (7H, m), 5.07 (1H, d, J=5.6 Hz), 5.17 (1H, d, J=3.1 Hz), 5.23 (1H, d, J=4.5 Hz), 5.54 (1H, d, J=5.9 Hz), 6.7–6.8 (3H, m), 7.0–7.4 (8H, m), 7.5–7.7 (4H, m), 7.70 (4H, s), 8.1–8.2 (2H, m), 8.51 (1H, d, J=7.0 Hz), 8.83 (1H, s)

FAB-MASS:m/z=1367.6 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{61}H_{77}N_8O_{23}SNa \cdot 6.5H_2O$:C 50.01, H 6.20, N 7.66 Found:C 50.30, H 6.50, N 7.75

Example 118

To a solution of The Object Compound (61) (0.25 g) in methanol (50 ml) was added dry 10% palladium on carbon (0.2 g) and stirred for 6 hours under hydrogen atmosphere. The palladium on carbon was filtered off, and the filtrate was

evaporated under reduced pressure to give Object Compound 118 (179 mg).

IR (KBr): 3400, 1668.1, 1627.6 cm^{-1}

NMR (DMSO-d_6, δ): 0.92 (3H, d, J=6.7 Hz), 1.1–2.45 (40H, m), 3.20 (3H, s), 3.28 (2H, t, J=6.5 Hz), 3.0–3.4 (1H, m), 3.5–4.7 (14H, m), 4.95–5.5 (12H, m), 6.55 (1H, d, J=8.4 Hz), 6.84 (1H, s), 6.86 (1H, d, J=8.4 Hz), 7.0–7.3 (4H, m), 7.9–8.3 (4H, m)

FAB-MASS:m/z=1292 (M+Na)

Elemental Analysis Calcd. for $C_{54}H_{88}N_9O_{22}SNa{\cdot}5H_2O$:C 47.67, H 7.26, N 9.26 Found:C 47.72, H 7.35, N 8.95

The Object Compounds (119) to (121) were obtained according to a similar manner to that of Example 118.

Example 119

NMR (DMSO-d_6, δ): 0.8 (3H, t, J=6.6 Hz), 1.00 (3H, d, J=7.3 Hz), 1.03 (3H, d, J=6.0 Hz), 1.2–1.5 (4H, m), 1.5–2.0 (5H, m), 2.1–2.7 (8H, m), 3.17 (1H, m), 3.6–4.5 (14H, m), 4.65–5.7 (12H, m), 6.72 (1H, d, J=8.1 Hz), 6.75 (1H, s), 6.80 (1H, d, J=8.1 Hz), 7.05 (1H, s), 7.1–7.7 (15H, m), 8.0–8.6 (4H, m), 8.85 (1H, s)

FAB-MASS:m/z=1274 (M+Na)

Elemental Analysis Calcd. for $C_{55}H_{74}N_9O_{21}SNa{\cdot}7H_2O$:C 47.93, N 6.43, N 9.15 Found:C 48.12, N 6.56, N 9.03

Example 120

IR (KBr): 3355.5, 1672.0, 1629.6 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.6 Hz), 0.98 (3H, d, J=6.5 Hz), 1.03 (3H, d, J=6.0 Hz), 1.2–2.6 (21H, m), 3.18 (1H, m), 3.6–4.5 (16H, m), 4.65–5.55 (12H, m), 6.6–7.5 (10H, m), 8.0–8.6 (4H, m), 8.89 (1H, s)

FAB-MASS:m/z=1256 (M+Na)

Example 121

IR (KBr): 3357.5, 1660.4, 1629.6, 1249.6 cm^{-1}

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.6 Hz), 0.96 (3H, d, J=6.8 Hz), 1.03 (3H, d, J=6.0 Hz), 1.1–1.5 (12H, m), 1.6–2.0 (5H, m), 2.0–2.5 (4H, m), 3.07 (1H, m), 3.5–4.5 (16H, m), 4.6–5.6 (12H, m), 6.72 (1H, d, J=8.1 Hz), 6.7–6.9 (4H, m), 7.04 (1H, s), 7.16 (1H, s), 7.1–7.5 (2H, m), 7.25 (2H, d, J=8.6 Hz), 8.0–8.2 (3H, m), 8.46 (1H, d, J=7 Hz), 8.84 (1H, s)

FAB-MASS:m/z=1256 (M+Na)

Elemental Analysis Calcd. for $C_{52}H_{76}N_9O_{22}SNa{\cdot}7H_2O$:C 45.91, H 6.67, N 9/27 Found:C 45.98, H 6.67, N 9.10

Example 122

A solution of Object Compound (11) (795 mg) in water (16 ml) was left for 240 hours. The solution was subjected to column chromatography on ODS (YMC-gel ODS-AMS50) and eluted with 25% CH_3CN/H_2O. The fractions containing Object Compound were combined and the acetonitrile was removed under reduced pressure. The residue was lyophilized to give Object Compound (123) (38 mg).

IR (KBr): 3361, 2956, 2875, 1668, 1627, 1521, 1249, 1047 cm^{-1}

NMR (DMSO-d_6, δ): 0.8–1.5 (19H, m), 1.6–2.4 (13H, m), 3.1–3.2 (1H, m), 3.5–4.1 (12H, m), 4.1–4.7 (10H, m), 4.9–5.6 (5H, m), 5.98 (1H, d, J=10.6 Hz), 6.36 (1H, d, J=10.6 Hz), 6.7–7.3 (12H, m), 7.4–8.0 (7H, m)

FAB-MASS:m/z=1273.1 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{55}H_{71}N_8O_{22}NaS{\cdot}11H_2O$:C 45.48, H 6.47, N 7.73 Found:C 45.83, H 6.26, N 7.75

The Object Compound (123) was obtained according to a similar manner to that of Example 118.

Example 123

IR (KBr): 3349.7, 1670.1, 1627.6 cm^{-1}

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=7.2 Hz), 0.96 (3H, d, J=6.7 Hz), 1.13 (3H, d, J=5.7 Hz), 1.18–1.55 (10H, m), 1.58–2.08 (5H, m), 2.08–2.90 (4H, m), 2.90–3.30 (2H, m), 3.60–4.50 (17H, m), 4.70–5.70 (12H, m), 6.65–7.60 (11H, m), 7.80 (2H, br s), 7.95–8.23 (2H, m), 8.75 (1H, d, J=7.0 Hz), 8.85 (1H, s)

FAB-MASS:m/z=1114.4 (M—SO_4—2)

Elemental Analysis Calcd. for $C_{52}H_{77}N_9O_{21}S{\cdot}6H_2O$:C 47.88, H 6.88, N 9.66 Found:C 47.60, H 6.74, N 9.53

The following compound (124) was obtained according to a similar manner to that of Example 1.

Example 124

IR (KBr): 3324, 2937, 2873, 1664, 1629, 1442, 1257 cm^{-1}

NMR (DMSO-d_6, δ): 0.91 (3H, t, J=7.1 Hz), 0.96 (3H, d, J=6.7 Hz), 1.09 (3H, d, J=5.7 Hz), 1.3–1.5 (4H, m), 1.7–2.6 (9H, m), 3.1–3.3 (1H, m), 3.7–4.6 (16H, m), 4.7–5.1 (7H, m), 5.11 (1H, d, J=5.6 Hz), 5.17 (1H, d, J=3.1 Hz), 5.26 (1H, d, J=4.5 Hz), 5.55 (1H, d, J=5.8 Hz), 6.7–6.9 (3H, m), 7.0–7.6 (6H, m), 7.97 (2H, d, J=8.8 Hz), 8.0–8.4 (6H, m), 8.85 (1H, s), 8.92 (1H, d, J=7.0 Hz)

FAB-MASS:m/z=1331 ($M+Na^+$)

Elemental Analysis Calcd. for $C_{55}H_{69}N_{10}O_{22}NaS_2$: C 45.45, H 5.89, N 9/64 Found: C 45.71, H 5.68, N 9.60

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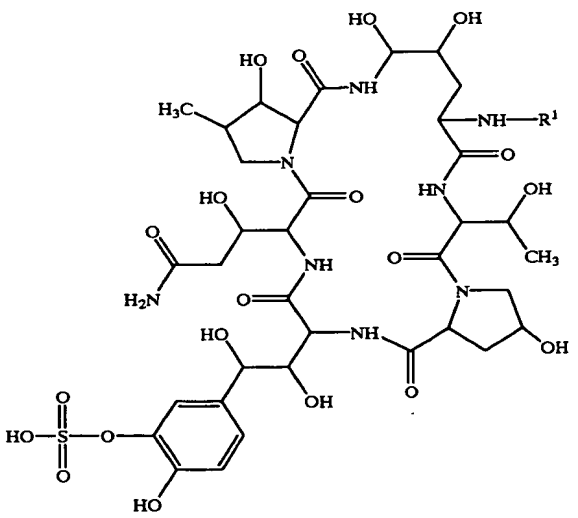
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What is claimed is:

1. A polypeptide compound of the following general formula (SEQ ID NO:1):

[I]



wherein R^1 is lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least ore oxygen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have one or more suitable substituent(s);

lower alkanoyl substituted with saturated 3 to 8 membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

ar(lower)alkenoyl substituted with aryl which may have one or more suitable substituent(s);

naphthyl(lower)alkenoyl which may have one or more higher alkoxy;

lower alkynoyl which may have one or more suitable substituent(s);

(C_2–C_6)alkanoyl substituted with naphthyl having higher alkoxy;

ar(C_2–C_6)alkanoyl substituted with aryl having one or more suitable substituent(s), in which, ar(C2–C6) alkanoyl may have one or more suitable substituent(s);

aroyl substituted with heterocyclic group which may have one or more suitable substituent(s), in which aroyl may have one or more suitable substituent(s);

aroyl substituted with aryl having lower alkoxy(higher) alkoxyl;

aroyl substituted with aryl having lower alkyl;

aroyl substituted with aryl having higher alkyl;

ar(lower)alkoxy(lower)alkanoyl which may have one or more suitable substituent(s);

arylamino(lower)alkanoyl which may have one or more suitable substituent(s);

lower alkanoyl substituted with pyrazolyl which has lower alkyl and aryl having higher alkoxy;

lower alkoxy(higher)alkanoyl, in which higher alkanoyl may have one or more suitable substituent(s);

aroyl substituted with cyclo(lower)alkyl having lower alkyl; indolylcarbonyl having higher alkyl;

naphthoyl having lower alkyl;

naphthoyl having higher alkyl;

naphthoyl having lower alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkoxy(lower) alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkoxy(lower) alkoxy;

aroyl substituted with aryl which has aryl having lower alkoxy(lower)alkoxy;

aroyl substituted with aryl having heterocyclicoxy (higher)alkoxy;

aroyl substituted with aryl having aryloxy(lower)alkoxy;

lower alkanoyl substituted with oxazolyl which has aryl having higher alkoxy;

higher alkanoyl having hydroxy;

higher alkanoyl having ar(lower)alkyl and hydroxy; or 3-methyl-tridecenoyl; and a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein

R^1 is lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl,

higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, 3 to 8-membered saturated heteromonocyclic group containing at least one nitrogen atom which may have phenyl having higher alkoxy, phenyl substituted with phenyl having lower alkoxy, 3 to 8-membered saturated heteromonocyclic group containing at least one nitrogen atom which may have phenyl having lower alkoxy(higher)alkoxy, 3 to 8-membered saturated heteromonocyclic group containing at least one nitrogen atom which may have phenyl having lower alkoxy, and oxo;

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenol having; lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have higher alkoxy, and oxo;

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atoms which may have 1 to 3 substituent(s) selected from the group containing of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo; or

lower alkanoyl substituted with saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo.

3. A compound of claim 1, wherein

R^1 is ar(lower)alkenoyl substituted with aryl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, lower alkoxy(lower)alkyl, halo(lower)alkoxy, lower alkenyloxy, halo(higher)alkoxy, lower alkoxy(higher)alkoxy, and oxo;

naphthyl(lower)alkenoyl which may have 1 to 1 higher alkoxy;

lower alkynoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

ar(C_2–C_6)alkanoyl substituted with aryl having 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, phenyl having lower alkoxy(lower)alkoxy, and oxo, in which ar(C_2–C_6)-alkanoyl may have hydroxy, oxo, protected amino or amino; or

(C_2–C_6)alkanoyl substituted with naphthyl having higher alkoxy.

4. A compound of claim 1, wherein

R^1 is aroyl substituted with heterocyclic group which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, phenyl having lower alkoxy(higher)alkoxy, phenyl having higher alkenyloxy, heterocyclic group substituted with phenyl having lower alkoxy, heterocyclic group, cyclo(lower)alkyl having phenyl, phenyl having cyclo(lower)alkyl, phenyl substituted with heterocyclic group having lower alkyl and oxo, cyclo(lower)alkyl having lower alkyl, phenyl substituted with phenyl having lower alkoxy, phenyl having heterocyclic group and oxo, in which aroyl may have halogen;

aroyl substituted with aryl having lower alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkyl; or aroyl substituted with aryl having higher alkyl.

5. A compound of claim 1, wherein

R^1

ar(lower)alkoxy(lower)alkanoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, phenyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo; or.

6. A compound of claim 1, wherein

R^1 is lower alkanoyl substituted with pyrazolyl which has lower alkyl and aryl having higher alkoxy;

lower alkoxy(higher)alkanoyl, in which higher alkanoyl may have amino or protected amino;

aroyl substituted with cyclo(lower)alkyl having lower alkyl;

indolylcarbonyl having higher alkyl;

naphthoyl having lower alkyl;

naphthoyl having higher alkyl;
aroyl substituted with aryl having lower alkoxy(lower) alkoxy(higher)alkoxy;
aroyl substituted with aryl having lower alkoxy(lower) alkoxy;
aroyl substituted with aryl which has phenyl having lower alkoxy(lower)alkoxy;
aroyl substituted with aryl having heterocyclicoxy (higher)alkoxy;
aroyl substituted with aryl having phenoxy(lower)alkoxy;
lower alkanoyl substituted with oxazolyl which has aryl having higher alkoxy;
higher alkanoyl having hydroxy;
higher alkenoyl having benzyl and hydroxy; or
3-methyl-tridecenoyl.

7. A compound of claim 2, wherein

R^1 is lower alkanoyl substituted with pyridyl or pyridazinyl, each of which may have 1 to 3 substituent (s) selected from the group consisting of higher alkoxy, higher alkoxy(lower)alkyl, phenyl having higher alkoxy, phenyl substituted with phenyl having lower alkoxy, piperazinyl substituted with phenyl having higher alkoxy, piperazinyl substituted with phenyl having lower alkoxy(higher)alkoxy, and piperazinyl substituted with phenyl having lower alkoxy;
lower alkanoyl substituted with coumarin which may have 1 to 3 substituent(s) selected from the group consisting of higher alkoxy, and oxo;
lower alkanoyl substituted with benzothiophenyl which may have 1 to 3 higher alkoxy;
lower alkanoyl substituted with benzofuranyl which may have 1 to 3 substituent(s) selected from the group consisting of higher alkoxy and lower alkyl;
lower alkanoyl substituted with benzooxazolyl which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl, phenyl having lower alkoxy, phenyl substituted with phenyl having lower alkyl, and pyridyl having higher alkoxy;
lower alkanoyl substituted with benzimidazolyl which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl, and phenyl having lower alkoxy; or
lower alkanoyl substituted with piperidyl or pierazinyl, each of which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having higher alkoxy, and naphthoyl having higher alkoxy.

8. A compound of claim 3, wherein

R^1 is phenyl(lower)alkenoyl substituted with phenyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, lower alkyl, higher alkyl, lower alkoxy(lower)alkyl, halo(lower)alkoxy, lower alkenyloxy, halo(higher)alkoxy, and lower alkoxy(higher)alkoxy;
naphthyl(lower)alkenoyl which may have 1 to 3 higher alkoxy;
lower alkynoyl which may have 1 to 3 substituent(s) selected from the group consisting of naphthyl having higher alkoxy, and phenyl substituted with phenyl having lower alkyl;
phenyl(C_2–C_6)alkanoyl substituted with phenyl which has 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, and phenyl having lower alkoxy (lower)alkyl,
in which phenyl (C_2–C_6)alkanoyl may have hydroxy, oxo, protected amino or amino; or
(C_2–C_6)alkanoyl substituted with naphthyl having higher alkoxy.

9. A compound claim 4, wherein

R^1 is benzoyl substituted with saturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkyl, phenyl having lower alkoxy(higher) alkoxy, phenyl having higher alkenyloxy, piperidyl substituted with phenyl having lower alkoxy, piperidyl, cyclo(lower)alkyl having phenyl, phenyl having cyclo (lower)alkyl, and phenyl substituted with triazolyl having oxo and lower alkyl,
in which benzoyl may have halogen;
benzoyl substituted with unsaturated 5-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkoxy(higher) alkoxy, and phenyl substituted with phenyl having lower alkoxy;
benzoyl substituted with 5 or 6-membered heteromonocyclic group containing 1 or 2 nitrogen atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl and phenol having lower alkoxy;
benzoyl substituted with 5-membered heteromonocyclic group containing 1 to 2 nitrogen atom(s) and 1 to 2 sulfur atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, cyclo (lower)alkyl having lower alkyl, phenyl substituted with phenyl having lower alkoxy, phenyl having cyclo (lower)alkyl, phenyl having piperidine, and phenyl having lower alkoxy(higher)alkoxy;
benzoyl substituted with phenyl having lower alkoxy (higher)alkoxy;
benzoyl substituted with phenol having lower alkyl; or
benzoyl substituted with phenyl having higher alkyl.

10. A compound of claim 5, wherein

R^1 is phenyl(lower)alkoxy(lower)alkanoyl which may have 1 to 3 higher alkoxy.

11. A compound of claim 1, wherein

R^1 is benzoyl substituted with piperazinyl which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkyl, phenyl having lower alkoxy(higher)alkoxy, phenyl having higher alkenyloxy, piperidyl substituted with phenyl having lower alkoxy, cyclo(lower)alkyl having phenyl, phenyl having cyclo(lower)alkyl, and phenyl substituted with triazolyl having oxo and lower alkyl, in which benzoyl may have halogen;
benzoyl substituted with isoxazolyl which may have 1 to 3 substituent(s) selected from the group consisting of higher alkyl, phenyl having higher alkoxy, phenyl having lower alkoxy(higher)alkoxy, and phenyl substituted with phenyl having lower alkoxy;
benzoyl substituted with phenyl having lower alkoxy (higher)alkoxy;
benzoyl substituted with phenyl having lower alkyl;
benzoyl substituted with phenyl having higher alkyl;
phenyl(lower)alkenoyl substituted with phenyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, lower alkyl, higher alkyl, lower alkoxy(lower)alkyl, halo(lower)alkoxy, lower alkenyloxy, halo(higher)alkoxy and lower alkoxy (higher)alkoxy;

benzoyl substituted with thiadiazolyl which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, cyclo(lower)alkyl having lower alkyl, phenyl substituted with phenyl having lower alkoxy, phenyl having cyclo(lower)alkyl, phenyl having piperidyl, and phenyl having lower alkoxy(higher) alkoxy; or

benzoyl substituted with oxadiazolyl which may have 1 to 3 substituent(s) selected from the group consisting of phenyl having lower alkoxy, phenyl having higher alkoxy, phenyl having lower alkoxy(higher)alkoxy, higher alkyl and phenyl substituted with phenyl having lower alkoxy.

12. A compound of claim 11, wherein

R^1 is benzoyl substituted with phenyl having lower alkoxy(higher)alkoxy; or

benzoyl substituted with phenyl having lower alkyl.

13. A compound of claim 11, wherein,

R^1 is benzoyl substituted with piperazinyl which may have phenyl having lower alkoxy;

benzoyl substituted with thiadiazolyl which may have phenyl having lower alkoxy(higher)alkoxy; or

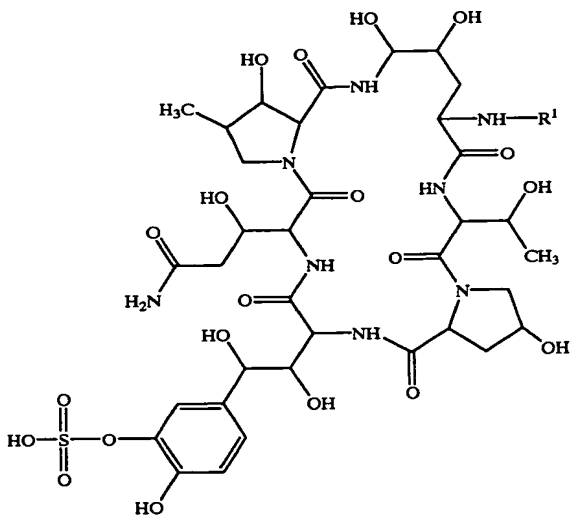
benzoyl substituted with oxadiazolyl which may have phenyl having lower alkoxy.

14. A compound of claim 11, wherein

R^1 is phenyl(lower)alkenoyl substituted with phenyl which may have lower alkoxy.

15. A process for the preparation of a polypeptide compound of the formula (SEQ ID NO:1):

[I]



wherein

R^1 is lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have one or more suitable substituent(s);

lower alkanoyl substituted with saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

ar(lower)alkenoyl substituted with aryl which may have one or more suitable substituent(s);

naphthyl(lower)alkenoyl which may have one or more higher alkoxy;

lower alkynoyl which may have one or more suitable substituent(s);

$(C_2–C_6)$alkanoyl substituted with naphthyl having higher alkoxy;

$ar(C_2–C_6)$alkanoyl substituted with aryl having one or more suitable substituent(s), in which $ar(C_2–C_6)$ alkanoyl may have one or more suitable substituent(s);

aroyl substituted with heterocyclic group which may have one or more suitable substituent(s), in which aroyl may have one or more suitable substituent(s);

aroyl substituted with aryl having lower alkoxy(higher) alkoxy;

aroyl substituted with 2 lower alkoxy;

aroyl substituted with aryl having lower vinyl;

aroyl substituted with aryl having higher alkyl;

ar(lower)alkoxy(lower)alkanoyl which may have one or more suitable substituent(s);

lower alkanoyl substituted with pyrazolyl which has lower alkyl and aryl having higher alkoxy;

lower alkoxy(higher)alkanoyl, in which higher alkanoyl may have one or more suitable substituent(s);

aroyl substituted with cyclo(lower)alkyl having lower alkyl;

indolylcarbonyl having higher alkyl;

naphthoyl having lower alkyl;

naphthoyl having higher alkyl;

aroyl substituted with aryl having lower alkoxy(lower) alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkoxy(lower) alkoxy;

aroyl substituted with aryl which has aryl having lower alkoxy(lower)alkoxy;

aroyl substituted with aryl having heterocyclicoxy (higher)alkoxy;

aroyl substituted with aryl having aryloxy(lower)alkoxy;

lower alkanoyl substituted with oxazolyl which has aryl having higher alkoxy;

higher alkanoyl having hydroxy;

higher alkanoyl having ar(lower)alkyl and hydroxy; or

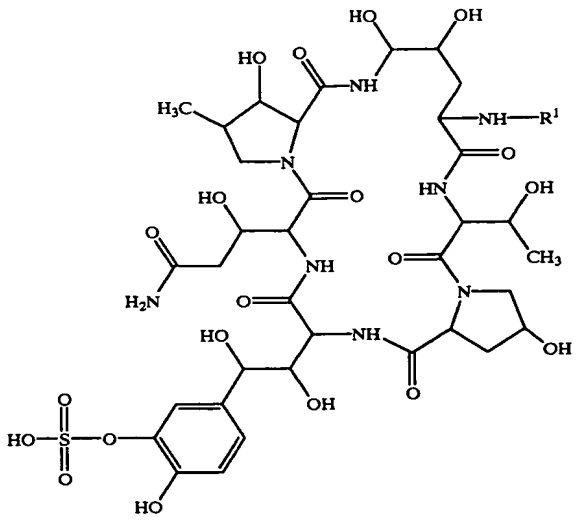
3-methyl-tridecenoyl; and

a pharmaceutically acceptable salt thereof,

which comprises

1) reacting a compound of the formula:

[I]



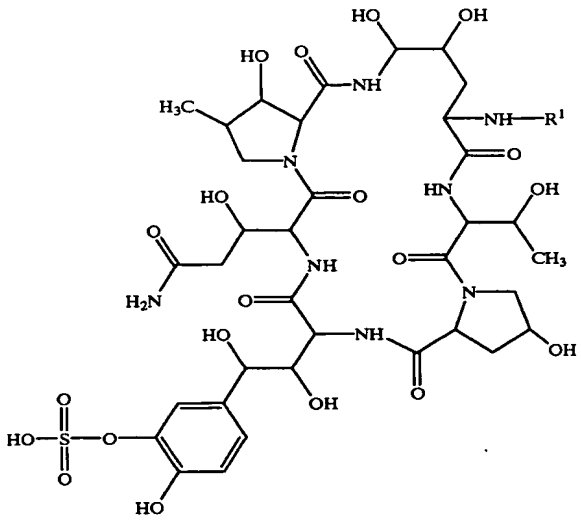
or its reactive derivative at the amino group or a salt thereof, with a compound of the formula:

R^1—OH

wherein R^1 is defined above,

or its reactive derivative at the carboxy group or a salt thereof, to give a compound of the formula:

[I]



wherein R^1 is defined above, or a salt thereof.

16. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers or excipients.

17. A method for the prophylactic and/or the therapeutic treatment of infectious diseases caused by pathogenic microorganisms which may comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

* * * * *

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Declaration, Power Of Attorney and Petition

D

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

CYCLIC HEXAPEPTIDES HAVING ANTIBIOTIC ACTIVITY

the specification of which

- ☐ is attached hereto.
- ☐ was filed on _____ as
 Application Serial No. _____
 and amended on _____.
- ☑ was filed as PCT international application
 Number PCT/JP95/01983
 on September 29, 1995,
 and was amended under PCT Article 19
 on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed	
9420425.2	G. Britain	07/10/94	☑ Yes	☐ No
9508745.8	G. Britain	28/04/95	☑ Yes	☐ No
			☐ Yes	☐ No
			☐ Yes	☐ No

We (I) hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	Filing Date	Status (pending, patented, abandoned)
PCT/JP95/01983	September 29, 1995	

And we (I) hereby appoint: Norman F. Oblon, Registration Number 24,618; Marvin J. Spivak, Registration Number 24,913; C. Irvin McClelland, Registration Number 21,124; Gregory J. Maier, Registration Number 25,599; Arthur I. Neustadt, Registration Number 24,854; Richard D. Kelly, Registration Number 27,757; James D. Hamilton, Registration Number 28,421; Eckhard H. Kuesters, Registration Number 28,870; Robert T. Pous, Registration Number 29,099; Charles L. Gholz, Registration Number 26,395; Vincent J. Sunderdick, Registration Number 29,004; William E. Beaumont, Registration Number 30,996; Steven B. Kelber, Registration Number 30,073; Robert F. Gnuse, Registration Number 27,295; Jean-Paul Lavalleye, Registration Number 31,451; Timothy R. Schwartz, Registration Number 32,171; Stephen G. Baxter, Registration Number 32,884; Martin M. Zoltick, Registration Number 35,745; Robert W. Hahl, Registration Number 33,893; Richard L. Treanor, Registration Number 36,379; Steven P. Weihrouch, Registration Number 32,829; John T. Goolkasian, Registration Number 26,142; Marc R. Labgold, Registration Number 34,651; William J. Healey, Registration Number 36,160; Richard L. Chinn, Registration Number 34,305; Steven E. Lipman, Registration Number 30,011; and Jacques M. Dulin, Registration Number 24,067; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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Date

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Date

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Signature of Inventor

Date

Residence:

Citizen of:

Post Office Address:

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Total number of pages including this page: 27

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OSMM&N File No. 270677US-18-18-0SD By: MJS/sli
Serial No. ____
Patent No. 5,376,634
6,107,458
6,265,536
In the matter of : FUJISAWA PHARMACEUTICAL CO., LTD.
For: Corporate Merger

- Credit Card Form for $120.00
- Commercial Register, Certified English Translation and Recordation Cover Sheet (PTO 1595) pages: 25

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Shaun Johnson

Total number of pages including this page: 27

Dept.: KLH

OSMM&N File No. 270677US-18-18-0SD By: MJS/slj

Serial No. ____

Patent No. 5,376,634
6,107,458
6,265,536

In the matter of : FUJISAWA PHARMACEUTICAL CO., LTD.

For: Corporate Merger

- Credit Card Form for $120.00
- Commercial Register, Certified English Translation and Recordation Cover Sheet (PTO 1595) pages: 25

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Atty Docket No.: 270677US-18-18-0SD

FORM PTO-1595
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To the Director of the United States Patent and Trademark Office. Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
FUJISAWA PHARMACEUTICAL CO., LTD.

Additional name(s) of conveying party(ies) attached? ☐ Yes ■ No

2. Name and address of receiving party(ies):
Name: ASTELLAS PHARMA INC.
Address: 3-11, Nihonbashi-Honcho 2-chome
Chuo-ku
Tokyo 103-8411
Japan

3. Nature of Conveyance:
☐ Assignment ■ Merger
☐ Security Agreement ☐ Change of Name
☐ Other
Execution Date: April 1, 2005

Additional name(s) and address(es) attached? ☐ Yes ☒ No

4. Application number(s) or patent number(s):
☐ This document is being filed together with a new application

A. Patent Application No.(s)

B. Patent No.(s)
5,376,634
6,107,458
6,265,536

Additional numbers attached? ☐ Yes ■ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Customer Number
22850
Tel. (703) 413-3000
Fax. (703) 413-2220

6. Total applications and patents involved: 3

7. Total fee (37 CFR 3.41): $120.00
■ Enclosed
☐ Authorized to be charged to deposit account

8. Deposit account number: 15-0030
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Marvin J. Spivak
Name of Person Signing

Signature

5/9/05
Date

Registration Number: 24,913

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CERTIFICATION

This is to certify that the following is, to the best of our knowledge and belief, a true and accurate translation into ENGLISH of the attached document(s) relating to:

Certificate of All Recorded Items in Commercial Register for Astellas Pharma Inc.

written in JAPANESE.

NEWTYPE COMMUNICATIONS, INC.

Sworn to and subscribed before me
this 6th day of May, 2005.

NOTARY PUBLIC

MICHAEL A. PRESTIA
Notary Public, State of New York
No. 01PR3157725
Qualified in Queens County
Commission Expires May 31, 2007

Certificate of All Recorded Items in Commercial Register

3-11 Nihonbashi-honcho 2-chome, Chuo-ku, Tokyo-to
Astellas Pharma Inc.
Corporation, etc. No. 0199-01-034966

Trade name	Yamanouchi Pharmaceutical Co., Ltd.	
	Astellas Pharma Inc.	Change made April 1, 2005
		Registered April 1, 2005
Head office	3-11 Nihonbashi-honcho 2-chome, Chuo-ku, Tokyo-to	
Publication method	Appearance in the Nihon Keizai Shimbun issued in Tokyo	
Access to information concerning balance sheet	http://www.yamanouchi.com/jp/index.html	Established March 25, 2003
		Registered April 1, 2003
	http://www.astellas.com/jp	Established April 1, 2005
		Registered April 1, 2005
Date of incorporation	March 20, 2002	
Purpose	1. Manufacture, sale, and import and export of pharmaceuticals, quasi-drugs, veterinary drugs, industrial chemicals, agricultural chemical, and other chemical products 2. Manufacture, sale, and import and export of food and food additives, condiments, feed and feed additives, cosmetics, hygiene items, medical devices, instrumentation, and miscellaneous everyday items 3. Manufacture, sale, and import and export of medical machinery and devices, industrial machinery and devices, and household machinery and devices 4. Manufacture, sale, and import and export of alcoholic beverages and beverage products 5. Raising, sale, and import and export of experimental animals 6. Buying and selling, leasing, management, and brokering of real estate 7. Warehousing and road transporting 8. Innkeeping and the management and administration of health and physical education facilities 9. Nonlife insurance agency business 10. Business of information processing services by computer 11. All business incidental to or related to the foregoing numbers	
	1. Manufacture, sale, and import and export of pharmaceuticals, quasi-drugs, veterinary drugs, reagents, industrial chemicals, agricultural chemical, and other chemical products 2. Manufacture, sale, and import and export of food and food additives, condiments, fertilizer, feed and feed additives, cosmetics, hygiene items, medical devices, veterinary medical devices, instrumentation, and miscellaneous everyday items 3. Buying and selling and import and export of natural products 4. Leasing and maintenance of medical devices 5. Manufacture, sale, import and export, leasing, and maintenance of medical machinery and devices, industrial machinery and devices, and household machinery and devices	

Reference No. u597415 * The underlined items have been expunged from the Register. 1/21

3-11 Nihonbashi-honcho 2-chome, Chuo-ku, Tokyo-to
Astellas Pharma Inc.
Corporation, etc. No. 0199-01-034966

Splitting-off of company	Split off October 1, 2004 into Zepharma Co., Ltd., 7-1 Nihonbashi-honcho 2-chome, Chuo-ku, Tokyo-to Registered October 1, 2004
Merger	Merger with Fujisawa Pharmaceutical Co., Ltd., 4-7 Doshomachi 3-chome, Chuo-ku, Osaka-shi Registered April 1, 2005
Matters concerning registration records	Pursuant to the provisions of 1989 Ministry of Justice Order No. 15, Supplementary Provisions, paragraph 3 Transcribed May 20, 1999

This is to certify that these are all the unclosed items recorded in the Register.

April 4, 2005

Tokyo Legal Affairs Bureau
Registrar: Motoyuki Oba (seal) [name partially obscured]

Reference No. u597415 *The underlined items have been expunged from the Register.

履歴事項全部証明書

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

商　号	山之内製薬株式会社	
	アステラス製薬株式会社	平成１７年　４月　１日変更 平成１７年　４月　１日登記
本　店	東京都中央区日本橋本町二丁目３番１１号	
公告をする方法	東京都において発行する日本経済新聞に掲載する	
貸借対照表に係る情報の提供を受けるために必要な事項	ｈｔｔｐ：／／ｗｗｗ．ｙａｍａｎｏｕｃｈｉ．ｃｏｍ／ｊｐ／ｉｎｄｅｘ．ｈｔｍｌ	平成１５年　３月２５日設定 平成１５年　４月　１日登記
	ｈｔｔｐ：／／ｗｗｗ．ａｓｔｅｌｌａｓ．ｃｏｍ／ｊｐ	平成１７年　４月　１日変更 平成１７年　４月　１日登記
会社成立の年月日	昭和１４年３月２０日	
目　的	１．医薬品、医薬部外品、動物用医薬品、工業薬品、農薬その他化学的製品の製造、販売および輸出入 ２．食品および食品添加物、調味料、飼料および飼料添加物、化粧品、衛生用具、医療用具、計量器、日用品雑貨の製造、販売および輸出入 ３．医療用機械器具、産業用機械器具、家庭用機器の製造、販売および輸出入 ４．酒精飲料および飲料品の製造、販売および輸出入 ５．実験動物の飼育・販売および輸出入 ６．不動産の売買、賃貸借、管理およびその仲介 ７．倉庫業および道路運送事業 ８．旅館業および保健体育施設の経営および管理 ９．損害保険代理業 １０．コンピューターによる情報処理サービス業 １１．前各号に付帯または関連する一切の事業	
	１．医薬品、医薬部外品、動物用医薬品、試薬、工業薬品、農薬その他化学的製品の製造、販売および輸出入 ２．食品および食品添加物、調味料、肥料、飼料および飼料添加物、化粧品、衛生用具、医療用具、動物用医療用具、計量器、日用品雑貨の製造、販売および輸出入 ３．天産物の売買ならびに輸出入 ４．医療用具の賃貸借および保守 ５．医療用機械器具、産業用機械器具、家庭用機器の製造、販売、輸出入、賃貸借および保守	

整理番号　ツ６０５０９８　　＊　下線のあるものは抹消事項であることを示す。　　

	６．医療に関連する各種科学的検査 ７．酒類、酒精飲料および飲料品の製造、販売および輸出入 ８．実験動物の飼育・販売および輸出入 ９．不動産の売買、賃貸借、管理およびその仲介 １０．倉庫業、道路運送事業および貨物利用運送事業 １１．旅館業および保健体育施設の経営および管理 １２．損害保険代理業 １３．出版業 １４．コンピューターの販売、賃貸借および保守 １５．コンピューターのソフトウェアの開発、販売および賃貸借 １６．コンピューターによる情報処理・提供サービス業 １７．経営コンサルタント業 １８．前各号に付帯または関連する一切の事業 平成１７年　４月　１日変更	平成１７年　４月　１日登記
一単元の株式の数	１０００株	
	１００株	平成１４年　４月　１日変更 平成１４年　４月　２日登記
発行する株式の総数	８億株	
	２０億株	平成１７年　４月　１日登記
発行済株式の総数並びに種類及び数	発行済株式の総数 ３億６１１５万２５２２株	平成１３年　４月３０日変更 平成１３年　５月　９日登記
	発行済株式の総数 ３億６１２０万３０５２株	平成１４年　２月２８日変更 平成１４年　３月１１日登記
	発行済株式の総数 ３億６１２０万３６０４株	平成１４年　４月３０日変更 平成１４年　５月１０日登記
	発行済株式の総数 ３億６１２１万４２６２株	平成１４年　５月３１日変更 平成１４年　６月１２日登記
	発行済株式の総数 ３億６１２１万６４７０株	平成１４年１２月３０日変更 平成１５年　１月１４日登記

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	発行済株式の総数 ３億６１２２万１５２３株	平成１６年　４月３０日変更 平成１６年　５月１３日登記
	発行済株式の総数 ３億６１５４万９９７１株	平成１６年１０月３１日変更 平成１６年１１月１０日登記
	発行済株式の総数 ３億６１９５万４２１５株	平成１７年　１月３１日変更 平成１７年　２月　８日登記
	発行済株式の総数 ５億７１４２万８００３株	 平成１７年　４月　１日登記
資本の額	金９９６億９４５６万３８４１円	平成１３年　４月３０日変更 平成１３年　５月　９日登記
	金９９７億４４５６万３８４１円	平成１４年　２月２８日変更 平成１４年　３月１１日登記
	金９９７億４５５６万３５１３円	平成１４年　４月３０日変更 平成１４年　５月１０日登記
	金９９７億５６５６万３１８５円	平成１４年　５月３１日変更 平成１４年　６月１２日登記
	金９９７億６０５６万１８７３円	平成１４年１２月３０日変更 平成１５年　１月１４日登記
	金９９７億６５５６万１８７３円	平成１６年　４月３０日変更 平成１６年　５月１３日登記
	金１０００億９０５６万１８７３円	平成１６年１０月３１日変更 平成１６年１１月１０日登記
	金１００４億９０５６万１８７３円	平成１７年　１月３１日変更 平成１７年　２月　８日登記

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

名義書換代理人の氏名及び住所並びに営業所	東京都港区芝三丁目３３番１号 中央三井信託銀行株式会社 東京都港区芝三丁目３３番１号 中央三井信託銀行株式会社　本店 平成１２年１２月　４日変更	平成１２年１２月　８日登記
役員に関する事項	取締役　小野田正愛	平成１３年　６月２８日重任 平成１３年　７月１０日登記 平成１５年　６月２７日退任 平成１５年　７月１１日登記
	取締役　竹中登一	平成１３年　６月２８日重任 平成１３年　７月１０日登記
	取締役　竹中登一	平成１５年　６月２７日重任 平成１５年　７月１１日登記 平成１７年　３月３１日辞任 平成１７年　４月　１日登記
	取締役　木村薫	平成１３年　６月２８日重任 平成１３年　７月１０日登記 平成１５年　６月２７日退任 平成１５年　７月１１日登記
	取締役　柿谷宗敏	平成１３年　６月２８日重任 平成１３年　７月１０日登記 平成１５年　６月２７日退任 平成１５年　７月１１日登記

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	取締役　髙山暢二	平成１３年　６月２８日重任
		平成１３年　７月１０日登記
	取締役　髙山暢二	平成１５年　６月２７日重任
		平成１５年　７月１１日登記
		平成１７年　３月３１日辞任
		平成１７年　４月　１日登記
	取締役　河石清	平成１２年　６月２９日重任
		平成１２年　７月１２日登記
		平成１４年　６月２７日退任
		平成１４年　７月１０日登記
	取締役　上田英彦	平成１２年　６月２９日重任
		平成１２年　７月１２日登記
	取締役　上田英彦	平成１４年　６月２７日重任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記
	取締役　鈴木弘	平成１２年　６月２９日重任
		平成１２年　７月１２日登記
		平成１４年　６月２７日退任
		平成１４年　７月１０日登記
	取締役　能浦栄蔵	平成１２年　６月２９日重任
		平成１２年　７月１２日登記
		平成１４年　６月２７日退任
		平成１４年　７月１０日登記

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	取締役　井上雅勝	平成１２年　６月２９日重任
		平成１２年　７月１２日登記
		平成１４年　６月２７日退任
		平成１４年　７月１０日登記
	取締役　田村隼也	平成１２年　６月２９日重任
		平成１２年　７月１２日登記
	取締役　田村隼也	平成１４年　６月２７日重任
		平成１４年　７月１０日登記
	取締役　田村隼也	平成１６年　６月２４日重任
		平成１６年　７月　７日登記
		平成１７年　３月３１日辞任
		平成１７年　４月　１日登記
	取締役　市川邦英	平成１２年　６月２９日重任
		平成１２年　７月１２日登記
	取締役　市川邦英	平成１４年　６月２７日重任
		平成１４年　７月１０日登記
	取締役　市川邦英	平成１６年　６月２４日重任
		平成１６年　７月　７日登記
		平成１７年　３月３１日辞任
		平成１７年　４月　１日登記
	取締役　髙橋重一	平成１３年　６月２８日重任
		平成１３年　７月１０日登記
	取締役　髙橋重一	平成１５年　６月２７日重任
		平成１５年　７月１１日登記
		平成１６年　６月２４日辞任
		平成１６年　７月　７日登記

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	取締役　畑中和義	平成１２年　６月２９日就任
		平成１２年　７月１２日登記
	取締役　畑中和義	平成１４年　６月２７日重任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記
	取締役　石井康雄	平成１２年　６月２９日就任
		平成１２年　７月１２日登記
	取締役　石井康雄	平成１４年　６月２７日重任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記
	取締役　佐羽俊男	平成１３年　６月２８日就任
		平成１３年　７月１０日登記
	取締役　佐羽俊男	平成１５年　６月２７日重任
		平成１５年　７月１１日登記
		平成１６年　６月２４日辞任
		平成１６年　７月　７日登記
	取締役　岸　功	平成１３年　６月２８日就任
		平成１３年　７月１０日登記
	取締役　岸　功	平成１５年　６月２７日重任
		平成１５年　７月１１日登記
		平成１６年　６月２４日辞任
		平成１６年　７月　７日登記

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	取締役　平岩廣章	平成１３年　６月２８日就任
		平成１３年　７月１０日登記
	取締役　平岩廣章	平成１５年　６月２７日重任
		平成１５年　７月１１日登記
		平成１６年　６月２４日辞任
		平成１６年　７月　７日登記
	取締役　柳沢勲	平成１３年　６月２８日就任
		平成１３年　７月１０日登記
	取締役　柳沢勲	平成１５年　６月２７日重任
		平成１５年　７月１１日登記
	取締役　柳澤勲	柳沢勲の氏
		平成１６年　３月１９日更正
		平成１６年　６月２４日辞任
		平成１６年　７月　７日登記
	取締役　臼田眞治	平成１４年　６月２７日就任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記
	取締役　杉崎生弥	平成１４年　６月２７日就任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記
	取締役　中島一	平成１４年　６月２７日就任
		平成１４年　７月１０日登記
		平成１６年　６月２４日退任
		平成１６年　７月　７日登記

整理番号　ツ６０５０９８　　＊　下線のあるものは抹消事項であることを示す。

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	取締役　宮崎石基	平成１５年　６月２７日就任 平成１５年　７月１１日登記 平成１６年　６月２４日辞任 平成１６年　７月　７日登記
	取締役　吉長孝二	平成１５年　６月２７日就任 平成１５年　７月１１日登記 平成１６年　６月２４日辞任 平成１６年　７月　７日登記
	取締役　長谷川忠夫	平成１５年　６月２７日就任 平成１５年　７月１１日登記 平成１６年　６月２４日辞任 平成１６年　７月　７日登記
	取締役　松尾眞 （社外取締役）	平成１６年　６月２４日就任 平成１６年　７月　７日登記 平成１７年　３月３１日辞任 平成１７年　４月　１日登記
	取締役　青木初夫	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	取締役　竹中登一	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	取締役　田村隼也	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	取締役　野木森雅郁	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	取締役　市川邦英	平成１７年　４月　１日就任 平成１７年　４月　１日登記

整理番号　ツ６０５０９８　　＊　下線のあるものは抹消事項であることを示す。　　

東京都中央区日本橋本町二丁目３番１１号
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	取締役　瀬島宏一	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	取締役　児島章郎 （社外取締役）	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	取締役　松尾眞 （社外取締役）	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	千葉県流山市野々下三丁目９３１番地の３５ 代表取締役　小野田正愛	平成１３年　６月２８日重任 平成１３年　７月１０日登記 平成１４年　６月２７日辞任 平成１４年　７月１０日登記
	千葉県流山市松ケ丘四丁目５０５番地の５６ 代表取締役　竹中登一	平成１３年　６月２８日重任 平成１３年　７月１０日登記
	東京都港区芝三丁目３４番１－１４０５号 代表取締役　竹中登一	平成１５年　３月１０日住所移転 平成１５年　３月１７日登記
	東京都港区芝三丁目３４番１－１４０５号 代表取締役　竹中登一	平成１５年　６月２７日重任 平成１５年　７月１１日登記 平成１７年　３月３１日退任 平成１７年　４月　１日登記
	東京都中央区日本橋浜町二丁目３番２－１２０２号 代表取締役　上田英彦	平成１５年　６月２７日就任 平成１５年　７月１１日登記 平成１６年　６月２４日退任 平成１６年　７月　７日登記

整理番号　ツ６０５０９８　　＊　下線のあるものは抹消事項であることを示す。　　１０／２１

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アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	埼玉県蓮田市緑町一丁目２１番１０号 代表取締役　田　村　隼　也	平成１６年１０月　１日就任 平成１６年１０月　１日登記 平成１７年　３月３１日退任 平成１７年　４月　１日登記
	大阪府池田市畑四丁目１３番３号 代表取締役　青　木　初　夫	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	東京都港区芝三丁目３４番１－１４０５号 代表取締役　竹　中　登　一	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	埼玉県蓮田市緑町一丁目２１番１０号 代表取締役　田　村　隼　也	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	大阪府高槻市真上町六丁目６５番２号 代表取締役　野　木　森　雅　郁	平成１７年　４月　１日就任 平成１７年　４月　１日登記
	監査役　日　巻　洋　之	平成１２年　６月２９日就任 平成１２年　７月１２日登記 平成１５年　６月２７日退任 平成１５年　７月１１日登記
	監査役　佐　々　木　典　夫	平成１２年　６月２９日就任 平成１２年　７月１２日登記
	監査役　佐　々　木　典　夫	平成１５年　６月２７日重任 平成１５年　７月１１日登記 平成１７年　３月３１日辞任 平成１７年　４月　１日登記
	監査役　立　川　四　郎	平成１２年　６月２９日就任 平成１２年　７月１２日登記 平成１５年　６月２７日退任 平成１５年　７月１１日登記

整理番号　ツ６０５０９８　　＊　下線のあるものは抹消事項であることを示す。　　１１／２１

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会社法人等番号　０１９９－０１－０３４９６６

	監査役　大谷豊達	平成１３年　６月２８日就任
		平成１３年　７月１０日登記
	監査役　大谷豊達	平成１６年　６月２４日重任
		平成１６年　７月　７日登記
		平成１７年　３月３１日辞任
		平成１７年　４月　１日登記
	監査役　山田英夫	平成１３年　６月２８日就任
		平成１３年　７月１０日登記
	監査役　山田英夫	平成１６年　６月２４日重任
		平成１６年　７月　７日登記
	監査役　斎藤健一郎	平成１５年　６月２７日就任
		平成１５年　７月１１日登記
	監査役　松尾眞	平成１５年　６月２７日就任
		平成１５年　７月１１日登記
		平成１６年　６月２４日辞任
		平成１６年　７月　７日登記
	監査役　石井政弥	平成１７年　４月　１日就任
		平成１７年　４月　１日登記
	監査役　小林幹司	平成１７年　４月　１日就任
		平成１７年　４月　１日登記
支　店	１ 東京都中央区日本橋本町二丁目４番７号	
		平成１４年　９月２８日移転
	東京都中央区日本橋本町二丁目５番７号	平成１４年１０月　４日登記
		平成１７年　１月２４日移転
	東京都中央区日本橋本町一丁目５番９号	平成１７年　２月　１日登記

整理番号　ツ６０５０９８　　＊　下線のあるものは抹消事項であることを示す。　　１２／２１

東京都中央区日本橋本町二丁目３番１１号
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	2 大阪市中央区北浜三丁目７番１２号	
	大阪市中央区瓦町三丁目６番５号	平成１５年　５月１９日移転 平成１５年　５月２１日登記
	3 北海道札幌市中央区大通西五丁目９番地１	
	4 名古屋市中区栄一丁目１０番２１号	
	名古屋市中区丸の内二丁目１番３６号	平成１７年　４月　１日移転 平成１７年　４月　１日登記
	5 宮城県仙台市青葉区大町二丁目２番２５号	
	6 福岡市博多区博多駅東一丁目１８番２５号	
	福岡市博多区下川端２番１号	平成１７年　４月　１日移転 平成１７年　４月　１日登記
	7 東京都中央区日本橋本町二丁目５番６号	
	東京都中央区日本橋本町一丁目５番９号	平成１７年　１月３１日移転 平成１７年　２月　１日登記
	東京都台東区東上野五丁目２４番８号	平成１７年　４月　１日移転 平成１７年　４月　１日登記
	8 香川県高松市寿町一丁目４番８号	
	香川県高松市サンポート２番１号	平成１６年　３月２２日移転 平成１６年　３月２２日登記
	9 広島県広島市中区大手町三丁目７番２号	
	広島市中区大手町二丁目１１番１０号	平成１７年　４月　１日移転 平成１７年　４月　１日登記

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１０ 台北市南京東路三段２８７号	平成１６年１０月３１日廃止 平成１６年１１月　１日登記
１１ 横浜市中区太田町六丁目８４番地２ 横浜市西区みなとみらい二丁目２番１号	平成１５年　２月２５日移転 平成１５年　３月　４日登記
１２ 京都市中京区烏丸通二条下る秋野々町５１３番地	
１３ 東京都中央区日本橋本町二丁目５番６号 東京都中央区日本橋本町一丁目５番９号	平成１７年　１月３１日移転 平成１７年　２月　１日登記
さいたま市大宮区桜木町一丁目７番地５	平成１７年　４月　１日移転 平成１７年　４月　１日登記
１５ 仙台市青葉区大町二丁目２番２５号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
１６ 東京都台東区東上野五丁目２４番８号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
１７ 千葉市美浜区中瀬二丁目６番地	平成１７年　４月　１日設置 平成１７年　４月　１日登記
１８ 東京都中央区日本橋本町一丁目５番９号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
１９ 名古屋市中区丸の内二丁目１番３６号	平成１７年　４月　１日設置 平成１７年　４月　１日登記

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	２０ 石川県金沢市本町一丁目５番２号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	２１ 大阪市中央区瓦町三丁目６番５号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	２２ 神戸市中央区磯辺通三丁目１番７号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	２３ 岡山市下石井一丁目１番３号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
	２４ 福岡市博多区下川端２番１号	平成１７年　４月　１日設置 平成１７年　４月　１日登記
新株予約権	第１回新株予約権 新株予約権の数 １４１０個 新株予約権の目的たる株式の種類及び数 当社普通株式　１４万１０００株 新株予約権１個当たりの目的たる株式の数（以下、「付与株式数」という。）は１００株とする。 なお、当社が当社普通株式の分割または併合を行う場合、次の算式により付与株式数を調整するものとし、調整の結果生じる１株未満の端数については、これを切り捨てるものとする。 調整後付与株式数　＝　調整前付与株式数　×　分割または併合の比率 また、当社が資本の減少、合併または会社分割を行う場合等、付与株式数の調整を必要とするやむを得ない事由が生じたときは、資本の減少、合併または会社分割の条件等を勘案のうえ、合理的な範囲で付与株式数を調整する。 各新株予約権の発行価額 無償	

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各新株予約権の行使に際して払込みをすべき金額

各新株予約権の行使に際して払込みをなすべき金額は、各新株予約権の行使により発行または移転する株式１株当たりの払込金額（以下、「行使価額」という。）に付与株式数を乗じた金額とする。

行使価額は、新株予約権を発行する日（以下、「発行日」という。）の属する月の前月の各日（取引が成立しない日を除く。）の東京証券取引所における当社普通株式の普通取引の終値（以下、「終値」という。）の平均値とし、１円未満の端数は切り上げる。ただし、その金額が発行日の終値（当日に終値がない場合は、それに先立つ直近日の終値）を下回る場合は、当該終値を行使価額とする。

なお、発行日以降、当社が時価を下回る価額で、当社普通株式につき、新株式を発行または自己株式を処分する場合（新株予約権の行使及び「商法等の一部を改正する法律」（平成１３年法律第１２８号）の施行前の商法に基づく転換社債の転換の場合を除く。）次の算式により行使価額を調整し、調整により生ずる１円未満の端数は切り上げる。

$$\text{調整後行使価額} = \text{調整前行使価額} \times \frac{\text{既発行株式数} + \dfrac{\text{新規発行株式数} \times \text{１株当たり払込金額}}{\text{時価}}}{\text{既発行株式数} + \text{新規発行株式数}}$$

上記の算式において、「既発行株式数」とは、当社の発行済株式数から当社が保有する自己株式数を控除した数とし、自己株式の処分を行う場合には、「新規発行株式数」を「処分する自己株式数」に読み替えるものとする。

また、発行日以降、当社が当社普通株式の分割または併合を行う場合には、行使価額は当該株式の分割または併合の比率に応じ比例的に調整されるものとし、調整により生ずる１円未満の端数は切り上げる。

さらに、発行日以降、当社が資本の減少、合併または会社分割を行う場合等、行使価額の調整を必要とするやむを得ない事由が生じたときは、資本の減少、合併または会社分割の条件等を勘案のうえ、合理的な範囲で行使価額を調整するものとする。

新株予約権を行使することができる期間

平成１７年７月１日から平成２５年６月２７日まで

新株予約権の行使の条件（払込価額及び行使期間を除く。）

各新株予約権の一部行使はできないこととする。

会社が新株予約権を消却することができる事由及び消却の条件

①当社が消滅会社となる合併契約書承認の議案が当社株主総会で承認された場合、または当社が完全子会社となる株式交換契約書承認の議案もしくは株式移転の議案につき当社株主総会で承認された場合は、当社は新株予約権を無償で消却することができるものとする。

②当社は、いつでも、当社が取得し保有する未行使の新株予約権を、無償にて消却することができるものとする。

平成１５年　７月１１日登記

第２回新株予約権
新株予約権の数
１４７０個

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

新株予約権の目的たる株式の種類及び数
当社普通株式１４万７０００株
新株予約権１個当たりの目的たる株式の数（以下、「付与株式数」という。）は１００株とする。
なお、当社が当社普通株式の分割または併合を行う場合、次の算式により付与株式数を調整するものとし、調整の結果生じる１株未満の端数については、これを切り捨てるものとする。
調整後付与株式数＝調整前付与株式数×分割または併合の比率
また、当社が資本の減少、合併または会社分割を行う場合等、付与株式数の調整を必要とするやむを得ない事由が生じたときは、資本の減少、合併または会社分割の条件等を勘案のうえ、合理的な範囲で付与株式数を調整する。
各新株予約権の発行価額
無償
各新株予約権の行使に際して払込みをすべき金額
各新株予約権の行使に際して払込みをなすべき金額は、各新株予約権の行使により発行または移転する株式１株当たりの払込金額（以下、「行使価額」という。）に付与株式数を乗じた金額とする。
行使価額は、新株予約権を発行する日（以下、「発行日」という。）の属する月の前月の各日（取引が成立しない日を除く。）の東京証券取引所における当社普通株式の普通取引の終値（以下、「終値」という。）の平均値とし、１円未満の端数は切り上げる。ただし、その金額が発行日の終値（当日に終値がない場合は、それに先立つ直近日の終値）を下回る場合は、当該終値を行使価額とする。
なお、発行日以降、当社が時価を下回る価額で、当社普通株式につき、新株式を発行または自己株式を処分する場合（新株予約権の行使、「商法等の一部を改正する法律」（平成１３年法律第１２８号）の施行前の商法に基づく転換社債の転換及び商法第２２１条ノ２の規定（単元未満株式の売渡請求）に基づく自己株式の譲渡の場合を除く。）は、次の算式により行使価額を調整し、調整により生ずる１円未満の端数は切り上げる。

$$\text{調整後行使価額} = \text{調整前行使価額} \times \frac{\text{既発行株式数} + \dfrac{\text{新規発行株式数} \times \text{１株当たり払込金額}}{\text{時価}}}{\text{既発行株式数} + \text{新規発行株式数}}$$

上記の算式において、「既発行株式数」とは、当社の発行済株式数から当社が保有する自己株式数を控除した数とし、自己株式の処分を行う場合には、「新規発行株式数」を「処分する自己株式数」に読み替えるものとする。
また、発行日以降、当社が当社普通株式の分割または併合を行う場合には、行使価額は当該株式の分割または併合の比率に応じ比例的に調整されるものとし、調整により生ずる１円未満の端数は切り上げる。
さらに、発行日以降、当社が資本の減少、合併または会社分割を行う場合等、行使価額の調整を必要とするやむを得ない事由が生じたときは、資本の減少、合併または会社分割の条件等を勘案のうえ、合理的な範囲で行使価額を調整するものとする。
新株予約権を行使することができる期間
平成１８年７月１日から平成２６年６月２４日まで
新株予約権の行使の条件（払込価額及び行使期間を除く。）
各新株予約権の一部行使はできないこととする。

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	会社が新株予約権を消却することができる事由及び消却の条件 ①当社が消滅会社となる合併契約書承認の議案が当社株主総会で承認された場合、または当社が完全子会社となる株式交換契約書承認の議案もしくは株式移転の議案につき当社株主総会で承認された場合は、当社は新株予約権を無償で消却することができるものとする。 ②当社は、いつでも、当社が取得し保有する未行使の新株予約権を、無償にて消却することができるものとする。 平成１６年　７月　７日登記
転換社債	第３回無担保転換社債 転換社債の総額 金１４９億２１００万円 金１４９億１５００万円 平成１３年　４月３０日変更　平成１３年　５月　９日登記 金１４９億１３００万円 平成１４年　４月３０日変更　平成１４年　５月１０日登記 金１４９億１１００万円 平成１４年　５月３１日変更　平成１４年　６月１２日登記 金１４９億３００万円 平成１４年１２月３０日変更　平成１５年　１月１４日登記 転換の条件 転換により発行する株式１株の発行価額（以下転換価額という。）は、下記(1)によって決定し、転換により発行すべき株式数は、次のとおりとする。ただし、本社債額面金額の一部及び利息については、転換を請求することはできない。 株式数＝各社債権者が転換請求のため提出した本社債額面金額の総額 ／ 転換価額 この場合に、１株未満の端数を生じたときは、その端数に相当する社債額面金額は、額面１００円につき１００円の割合で償還する。 (1)　転換価額　金４４１３円 (2)　転換価額の調整 転換価額は、当社が本社債発行後、時価を下回る払込金額で新株式を発行する場合には、次の算式により調整される。 調整後転換価額 ＝ 調整前転換価額 ×（既発行株式数＋新発行株式数×１株当りの払込金額／時価）／（既発行株式数＋新発行株式数） なお、株式配当、無償交付、株式の分割もしくは併合等が行われる場合にも調整されるものとする。ただし、転換により当社記名式額面普通株式を発行する場合で、調整後の転換価額が当社記名式額面普通株式の額面金額を下回るときは、当該額面金額を転換価額とする。 転換によって発行すべき株式の内容 当社記名式額面普通株式（１株の額面金額５０円） ただし、本社債の転換により発行する株式を当社記名式無額面普通株式とした場合は、当社記名式無額面普通株式。

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

	転換の請求をすることのできる期間 昭和６２年９月１日から昭和７７年１２月３０日まで 各転換社債の金額 金１００万円 各転換社債につき払い込んだ金額 全額 本社債はこれを株式に転換することができる
	平成１４年１２月３０日転換請求期間満了 平成１５年　１月１４日登記
	２０１４年満期円貨建転換社債 転換社債の総額 金１８８億８０００万円 金１８６億８０００万円 平成１１年　５月３１日変更　平成１１年　６月１４日登記 金１７６億９０００万円 平成１１年　６月３０日変更　平成１１年　７月１２日登記 金１１２億３０００万円 平成１１年　７月３１日変更　平成１１年　８月１０日登記 金１０５億４０００万円 平成１１年　８月３１日変更　平成１１年　９月１３日登記 金９６億５０００万円 平成１１年１０月３１日変更　平成１１年１１月１２日登記 金９４億４０００万円 平成１１年１１月３０日変更　平成１１年１２月１３日登記 金９２億２０００万円 平成１１年１２月３１日変更　平成１２年　１月１４日登記 金９１億８０００万円 平成１２年　１月３１日変更　平成１２年　２月１４日登記 金８３億９０００万円 平成１２年　２月２９日変更　平成１２年　３月１４日登記 金８１億５０００万円 平成１２年　４月３０日変更　平成１２年　５月１２日登記 金８１億４０００万円 平成１２年　５月３１日変更　平成１２年　６月１３日登記 金７５億１０００万円 平成１２年　７月３１日変更　平成１２年　８月　８日登記 金７２億９０００万円 平成１２年　８月３１日変更　平成１２年　９月１１日登記 金６６億４０００万円 平成１２年１１月３０日変更　平成１２年１２月　８日登記 金６６億１０００万円 平成１２年１２月３１日変更　平成１３年　１月１２日登記 金６６億円 平成１３年　１月３１日変更　平成１３年　２月　８日登記 金６５億円 平成１４年　２月２８日変更　平成１４年　３月１１日登記 金６４億８０００万円 平成１４年　５月３１日変更　平成１４年　６月１２日登記

整理番号　ツ６０５０９８　　＊　下線のあるものは抹消事項であることを示す。　　１９／２１

東京都中央区日本橋本町二丁目3番11号
アステラス製薬株式会社
会社法人等番号　0199－01－034966

	金64億7000万円 平成16年　4月30日変更　平成16年　5月13日登記 金58億2000万円 平成16年10月31日変更　平成16年11月10日登記 金50億2000万円 平成17年　1月31日変更　平成17年　2月　8日登記 転換の条件 本社債は、その額面金額に対し、下記の転換価額につき当社額面普通株式1株の割合をもって当社額面普通株式に転換することができる。 但し、転換の際に生じる1株未満の端数は、これを切り捨て、現金による調整は原則として行わない。 イ．当初の転換価額は、1株当り金1979円とする。 ロ．転換価額の修正 1998年3月31日、2004年3月31日及び2009年3月31日（以下それぞれ「決定日」という。）より東京証券取引所における当社額面普通株式の普通取引の終値のある45連続営業日前に開始する30連続営業日における終値の平均値に1．025を乗じ1円未満を切り上げた額が、当該各決定日に有効な転換価額を1円以上下回る場合には、転換価額は1998年4月22日、2004年4月22日及び2009年4月22日（以下それぞれ「効力発生日」という。）以降、上記により算出された各金額（但し、決定日から効力発生日の前日までに効力の発生した下記ハ．の調整を受ける。）に修正されるものとする。但し、転換価額は、かかる修正の結果として当初の転換価額（但し、下記ハ．の調整がなされた場合には、調整後の金額）の50％未満に修正されることはなく、50％未満となる場合は、かかる転換価額の50％にあたる金額の1円未満を切り上げた価額とする。 ハ．転換価額の調整 転換価額は、当社が本社債発行後、当社の普通株式の時価を下回る払込金額で新たに普通株式を発行する場合、次の算式により調整される。 $$\text{調整後転換価額} = \text{調整前転換価額} \times \frac{\text{既発行株式数} + \dfrac{\text{新発行株式数} \times \text{1株当り払込金額}}{\text{1株当り時価}}}{\text{既発行株式数} + \text{新発行株式数}}$$ 又、転換価額は、株式の分割・併合、当社の普通株式の時価を下回る当初転換価額又は新株引受権行使価額での転換社債又は新株引受権付社債の発行その他一定の場合にも適宜調整される。但し、転換価額は当社額面普通株式の額面金額を下回らないものとする。 転換によって発行すべき株式の内容 当社額面普通株式（現在の1株の額面金額50円） 転換の請求をすることのできる期間 1994年5月9日から2014年3月24日の営業終了時（転換請求地時間）までとする。 各転換社債の金額 金1000万円 各転換社債につき払い込んだ金額 全額 本社債はこれを株式に転換することができる。

東京都中央区日本橋本町二丁目３番１１号
アステラス製薬株式会社
会社法人等番号　０１９９－０１－０３４９６６

会社分割	平成１６年１０月１日東京都中央区日本橋本町二丁目７番１号ゼファーマ株式会社に分割 平成１６年１０月　１日登記
吸収合併	大阪市中央区道修町三丁目４番７号藤沢薬品工業株式会社を合併 平成１７年　４月　１日登記
登記記録に関する事項	平成元年法務省令第１５号附則第３項の規定により 平成１１年　５月２０日移記

これは登記簿に記録されている閉鎖されていない事項の全部であることを証明した書面である。

平成１７年　４月　７日
東京法務局
登記官　　大　庭　元　行

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